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Cost-efficacy vs. cost-effectiveness:

the case of inhaled corticosteroids in the treatment of asthma

par

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Summary

Objective. This thesis deals with the issue of the construct (external) validity of cost measurement during clinical trials (RCTs) using the example of inhaled corticosteroid (iCST) treatment for asthma. The example is used to explore in particular aspects of the differences in the constructs of setting, treatment and subject on the costs estimated under conditions of RCT and those estimated under conditions of normal clinical practice. **Hypotheses**. In the RCT: 1) the use and cost of health services will be less variable; (2) the net total cost (of health services other than that of iCST) will be lower; and (3) the use and cost of iCST therapy will be higher than in real life. The outcome effect of the RCT as measured by the use and cost of health services is a result of the iCST treatment, the other factors which constitute the RCT construct, and their interaction. **Methodology**. Two samples of persons with asthma were recruited, subjects who had participated in RCTs involving iCSTs (TS), and subjects using iCSTs who had never so participated (NS). Their use and cost of asthma-related health services (medications, physician visits, emergency department visits and hospitalisations) were estimated and compared. In the TS services were measured during and outside the RCT. The effect of having participated in a trial is examined, by comparing the two samples (TS vs. NS) in 'real life'. In a second approach, age and gender differences in the subject construct are controlled for by adjusting the results to an index population, that of Canadian asthmatics. **Results**. (1) In the TS the 'real life' measure showed greater variance than the trial measure.

Variance between the two samples was in all cases higher in the NS than the TS. (2) There were lower net Total costs in the TS in the trial setting than in the normal setting. The TS were less likely than the NS to have higher ($250 or more) net Total costs than the NS (OR 0.3, 85%CI 0.2 – 0.5). (3) The costs of iCSTs in the TS were considerably higher in the trial setting than the normal setting, and higher in the TS than the NS (OR 3.3, 85%CI 1.5 – 7.3). Age and gender adjusted estimates of total cost were approximately $592 for the NS, $771 for the TS in the normal setting, and $859 per year for the TS in the trial setting. The same calculation for net Total cost in the normal setting was $520 (TS) and $451 (NS), and in the trial setting it was $245 (TS). **Conclusions**. The hypotheses are generally confirmed. The use and cost differences are consistent with differences in 1) treatment construct (practices which encourage better adherence medication, and regular follow-up visits), 2) subject construct (selection for individuals adherent to their therapy and participation in an RCT) and the setting construct (free medications in the RCT). No difference in total anti-asthma costs between the two groups was seen, because of the large variance in total costs in the NS and because cost differences in iCST balanced that of net Total costs. **Implications**. The results of this study show it is difficult to use RCT generated cost information to model cost-effectiveness information with respect to the treatment of moderate and severe, stable, asthma.

Résumé

Cette thèse traite de la problématique de la validité de construit (validité externe) des essais cliniques randomisés (ECRs), lorsque l'objet visé est d'estimer les coûts associés à un traitement. Pour ce faire, l'exemple du traitement de l'asthme par les corticostéroïdes inhalés (CSTis) a été choisi. A l'aide de cet exemple, les différences entre les coûts estimés dans le cadre d'un ECR et ceux estimés dans un contexte de pratique clinique usuelle *(milieu réel)* ont été établies. Elles ont été discutées en faisant référence aux différences existant entre l'ECR et le milieu réel en ce qui a trait aux construits d'environnement (*setting*), de traitement (*treatment*) et de sujet (*subject*).

Une revue de la littérature sur la validité de construit est présentée suivi d'une discussion sur les problèmes associés à l'extrapolation des données produites dans le cadre d'ECR, particulièrement en ce qui concerne les données de coûts. Un modèle est proposé pour l'analyse de la validité de construit associée à la mesure de coûts obtenue d'un ECR.

Puisque le travail empirique utilise le traitement de l'asthme par CSTi comme exemple, la littérature concernant ce traitement est revue en insistant plus particulièrement sur les aspects pharmacoéconomiques et les difficultés d'application de l'évaluation économique à cette maladie.

Suite à la revue de la littérature, et considérant que les ECRs et le milieu réel diffèrent en termes des construits d'environnement, de sujet et de traitement et que l'utilisation et les coûts des services de santé sont liés à ces construits et à leur interaction, les hypothèses suivantes ont été proposées :

Dans l'essai clinique randomisé :

- l'utilisation et le coût des services de santé seront moins variables qu'en milieu réel ;
- le coût total des services de santé excluant le coût des CSTis sera moindre qu'en milieu réel ;
- l'utilisation et le coût de la thérapie par CSTi seront plus élevés qu'en milieu réel.

En conséquence, les données d'utilisation et de coûts tirés des ECRs peuvent difficilement être généralisées au milieu réel.

Afin de vérifier ces hypothèses, deux échantillons de patients asthmatiques furent recrutés. Le premier groupe est constitué de sujets ayant déjà participé à un ECR impliquant l'utilisation de CSTi (groupe TS). Le second groupe comprend des personnes utilisant des CSTis mais n'ayant jamais participé à

une telle étude (groupe NS). L'utilisation par ces patients des services de santé reliés à leur condition asthmatique (médicaments, visites médicales, visites à un service d'urgence, et hospitalisations) et les coûts qui y sont associés furent mesurés.

Le recrutement des patients du premier groupe a débuté par l'identification des ECRs menés au Québec de 1990 à mars 1997 et impliquant l'utilisation de CSTi. Huit ECRs ont été ainsi identifiés. Ces ECRs impliquaient 254 sujets qui prenaient des CSTis, dont 154 ont accepté de participer à l'étude.

Les sujets du second groupe ont été recrutés par les pharmaciens communautaires parmi leur clientèle de personnes utilisant des CSTis. Pour être admissibles à l'étude, les sujets devaient rapporter avoir reçu un diagnostic d'asthme et n'avoir jamais participé à un ECR.

L'utilisation des services de santé reliés à l'asthme (médicaments antiasthmatiques, visites médicales, visites à l'urgence et hospitalisations pour l'asthme) était déterminée à partir des dossiers de l'ECR, des dossiers des pharmacies, des banques de données de la Régie d'Assurance maladie du Québec (RAMQ) et de la banque des données d'hospitalisations (MEDECHO). Pour les personnes du groupe TS, ces services ont été comptabilisés pendant la période d'ECR et pour une période n'excédant pas 6 mois adjacents à la période de l'ECR. Pour les personnes du groupe NS, ces

services ont été comptabilisés pour un période d'utilisation n'excédant pas 6 mois.

Il ne fut pas possible de colliger toute l'information sur la médication utilisée en milieu ambulatoire par les 154 patients du groupe TS ; cependant, nous l'avons obtenue pour 71 de ces patients pour la période de l'ECR, et pour 75 d'entre eux hors de cette période. Par ailleurs, une information complète sur l'utilisation des ressources a été obtenue pour 51 des 52 patients du groupe NS.

L'examen des différences entre le contexte des ECR et le milieu réel a été réalisé en deux étapes. La première étape a consisté à comparer l'utilisation et le coût des services de santé chez les personnes du groupe TS en cours d'essai à ceux observés chez les mêmes personnes hors de la période d'essai clinique. Dans une seconde étape, on a étudié l'effet de la participation à un essai clinique, en comparant les patients du groupe TS hors de la période des ECRs aux patients du groupe NS (en milieu réel par définition). La validité de construit des ECRs a aussi été examinée en comparant le groupe TS en cours d'essai clinique au groupe NS. Par ailleurs, des comparaisons ont également été effectuées en ajustant les résultats par le biais d'une standardisation pour l'âge et le sexe utilisant la population asthmatique canadienne comme population de référence. Étant donné la

nature exploratoire de cette étude, un seuil de signification statistique de 0.15 a été retenu pour l'erreur α.

L'hypothèse concernant la variance de l'utilisation et les coûts des services de santé a été vérifiée. Ainsi, pour presque toutes les comparaisons effectuées au sein du groupe de sujets ayant participé à un essai clinique (groupe TS), on a noté une plus grande variance des mesures en milieu réel qu'en cours d'essai clinique (à l'exception des visites médicales totales ambulatoires où les variances étaient presque identiques). Dans le cas des comparaisons entre les groupes TS et NS, la variance était systématiquement plus élevée dans le groupe NS que dans le groupe TS.

Les coûts totaux reliés à l'asthme dans le groupe TS ont été plus élevés en cours d'ECR que hors de la période d'ECR, cette différence résultant surtout des coûts plus élevés des CSTis en cours d'essai clinique ($p<0.01$). On a observé dans le groupe TS en cours d'essai clinique des coûts moyens moindres que hors essai pour tous les autres services de santé reliés à l'asthme ($p<0.01$). Ces résultats sont compatibles avec nos deuxième et troisième hypothèses.

Comparativement au groupe NS, on a observé dans le groupe TS hors de la période d'essai clinique des différences pour certaines catégories de services, dont les coûts des CSTis (TS > NS, $p=0.01$), les visites à un service d'urgence

(TS < NS, p<0.01), les visites auprès de médecins omnipraticiens (TS < NS, p<0.01). Ces résultats vont également dans le sens de nos hypothèses. Les coûts totaux reliés à l'asthme des groupes TS et NS n'ont cependant pas démontré de différence statistiquement significative.

Les résultats des analyses multivariées supportent également nos hypothèses. Ainsi, l'analyse de régression logarithmique ajustée pour le sexe et le milieu géographique (villes de Montréal ou de Québec), a révélé que la probabilité d'afficher des coûts totaux (excluant le coût des CSTis), égaux ou supérieurs à 250$/an, était plus faible dans le groupe TS en cours d'ECR que dans le groupe NS (OR 0.3, 85%CI 0.2 - 0.5).

En utilisant une autre méthode de comparaison, celle d'ajuster pour l'âge et le sexe à une population indexe, soit la population asthmatique canadienne, les coûts annuels pour l'ensemble des services de santé reliés à l'asthme ont été estimés à $592 en moyenne en milieu réel pour un sujet n'ayant jamais participé à un essai clinique (groupe NS), et de $771 s'il a déjà participé à un essai clinique (groupe TS hors de la période d'essai). En comparaison, les coûts ajustés pour un patient en cours d'essai clinique sont plus élevés à $859 mais les différences ne sont pas statistiquement significatives. Lorsqu'on a exclu le coût du CSTi du coût total, les valeurs ajustées étaient de $520 pour le groupe TS hors de la période d'essai et de $451 pour le groupe NS. Ces valeurs sont considérablement plus élevées que celles estimées ($245) pour

le groupe TS en cours d'essai clinique, et ces différences sont statistiquement significatives ($p<0.10$).

On note donc des coûts associés aux CSTis plus élevés durant l'essai clinique qu'en contexte réel. Cependant les autres coûts associés au traitement de l'asthme sont plus faibles en condition d'essai qu'en condition réelle. Tout se passe comme si le contexte de l'essai favorisait un recours plus soutenu aux CSTis. Ce recours plus soutenu mène à des coûts plus élevés associés à ces médicaments. Cependant, il se traduit aussi par un meilleur contrôle de la maladie avec pour conséquence une diminution des coûts des traitements autres que les CSTis.

L'influence du contexte de l'essai semble claire. Cette influence peut être rattachée aux particularités des construits de l'ECR. Les différences de construit relatif au sujet jouent un rôle important : la sélection de patients particulièrement fidèles à leur traitement pourrait expliquer l'usage plus marqué de CSTi, chez les patients ayant participé à un essai clinique comparativement à ceux qui n'y ont jamais participé. L'existence de différences lorsqu'on compare la situation des patients d'ECR en dehors de la période d'essai clinique à celle des patients du groupe NS, indique qu'il y a des différences inhérentes au sujet. Outre les différences relatives à l'adhésion au traitement on peut également penser que les patients choisis

pour les essais sont mieux informés, plus intéressés à leur traitement, plus souvent suivis par un spécialiste du domaine.

Pour ailleurs, l'existence de différences entre les périodes hors-essai et intra-essai chez les même sujets nous permet d'affirmer que l'influence de l'essai dépasse celui de la sélection des sujets et peut être liée au fait que le construit 'environnement' et en particulier le construit 'traitement' de l'ECR et du milieu réel ne sont pas les mêmes. Ainsi dans l'ECR, le protocole de traitement nécessite que le patient se rapporte aux investigateurs et inscrive quotidiennement sur une fiche l'usage de sa médication, ce qui est susceptible d'encourager l'adhésion à la médication anti-inflammatoire. La surveillance (*monitoring*) étroite du patient par les professionnels de la santé impliqués dans l'essai clinique, de même que les visites régulières exigées selon le protocole de l'essai, peuvent agir comme substituts aux visites médicales susceptibles de survenir en milieu réel.

Notre étude met en doute la capacité de l'ECR à fournir des données d'utilisation et de coûts, qui peuvent être utilisées pour estimer le (rendement) coût-efficacité en milieu réel. Dans le cas du traitement de l'asthme, nos analyses révèlent que les estimations tirées des ECRs sur-estiment les coûts des CSTis par rapport à ce que l'on observerait en milieu réel. En revanche, elles sous-estiment le coût des médicaments d'appoint de même que des autres services de santé reliés à l'asthme. Bien que notre étude porte sur un

petit échantillon de patients stables atteints d'asthme modéré à sévère, on peut présumer que la même problématique s'applique à d'autres maladies chroniques. Il convient donc d'user de prudence lorsqu'on veut prendre des décisions quant à l'allocation des ressources en se basant sur des données d'efficience tirées d'essais cliniques.

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List of Abbreviations

Beta-2	bonchodlilator (beta-agonists)
CI	confidence interval
FDA	Food and Drug Administration (USA)
FEV_1	forced expiratory volume
iCST	inhaled corticosteroid
L	litre
mg	milligram
MSSS	Ministère de la Santé et des services sociaux du Québec
NS	normal setting sample
NTP	non-trial period
OR	odds ratio
PEF(R)	peak expiratory flow (rate)
Pred	predicted
RAMQ	Régie de l'assurance maladie du Québec
RCT	randomised clinical trial
SD	standard deviation
SFD	symptom-free day
TP	trial period
TS	trial sample
µg	microgram
TP	trial period

Dedication

'She wanted more vigorous measures, a more complete reformation, a quicker release from debt, a much higher tone of indifference for everything but justice and equity.' (Jane Austin, Persuasion)

I find myself at the end of this project which has endured so long, and which has consumed such a huge portion of my life, emotionally, intellectually and physically. It is vital to stop and take a few hours to think back on the process, to remember and thank all those who have helped me so much to realise this work, which is truly one of the major investments of my life.

This doctorate had been a gift - from myself, from my family, my colleagues, my advisors, but most of all from my husband. The time and the energy which we have all put into the preparation, the planning, the analysis, the writing, the comments, the suggestions, and the rewriting, are only summarised in the following pages. The majority of the efforts have left faint traces along the way and will be shortly (almost) forgotten.

I wish to thank all of you for this gift.

First, my family. Robert, with his amazing energy, his positive encouragement and his unqualified support. Certainly this gift is mostly his, and I cannot know how to thank him. (Cleaning up the office and filing all the documents will be a small beginning.) My parents, who always believed in me, and whose quiet (and not so quiet) pride in their daughter and their constant interest are the basis for my capacity to do things. The children in my life: my grandchildren: Camille, Charlotte and Cassandre, who have lightened many mornings and evenings with laughter and distraction; my delightful nephew William who never stops asking questions and reminds my parents of me at his age. Charles & Sylvie who provide expert help, and loan us their kids when needed, and Lysanne and Jérôme who are kind and cute and too far away to loan us theirs very often. 'Thers' who keeps up our spirits, serves as a great example, and makes the best ragout de boulette and lemon meringue pie in the world.

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everything is right and everything makes sense. She has kept me focussed. Finally, Lucien Abenhaim who was a great help early on.

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This thesis is dedicated to you all, but most of all to my *Menum*. Thankyou.

Chapter 1

General Introduction

This thesis explores the issue of the construct (external) validity of cost measurement during clinical trials (RCTs) using the example of inhaled corticosteroid (iCST) treatment for asthma. The issue of the ability to generalise RCT data has been discussed often in the pharmacoeconomic literature. The approach to the topic uses the well-known social-sciences framework of construct validity, and the case study involves a well-established and effective treatment (iCSTs) in a chronic disease (asthma) with important health and economic consequences.

The thesis begins with a review of the literature on construct validity and a discussion of the problems associated with generalisation of RCT data, particularly as concerning cost data. A model for the analysis of construct validity as it affects the measure of cost in RCTs is developed. As the examination of this issue is conducted using the chronic disease of asthma treated by iCSTs, the thesis then reviews the literature on the burden of asthma and its treatment. The published literature in the field of pharmacoeconomics in asthma is also reviewed, highlighting the problems for this type of analysis in the chronic disease of asthma.

The case study is used to explore the differences in the costs estimated under conditions of RCT and those estimated under conditions of normal clinical practice. We are trying to differentiate the effect of the drug itself from the other factors which constitute the RCT construct. The use of health services is first measured in units before being translated into cost. The analyses of cost differences are broken down into two parts. First the differences of cost associated with the setting itself is looked at, keeping the individuals selected constant. Secondly the effect of having been chosen for and participated in a trial and having never participated is examined. The two are then merged, and the trial subjects in the trial setting are compared to subjects treated in real life.

The research should allow the better understanding of the research protocol of the RCT and its relationship to 'real life' economic evaluation. It could enable more balanced application and interpretation of the results of economic evaluations conducted during clinical trials of iCSTs, with respect to their cost and use of health resources outcomes, to the conditions of the use of those medications in the general population in the pharmaceutical treatment of asthma.

1.1 Aims and outline of the thesis

In this thesis, the following questions are posed and answered:

1. Given that we cannot easily generalise the measures of use and cost of health services from the RCT to those in real life, what does the literature tell us of the factors that are responsible for differences in those measures, and how they can be better understood?
2. What is known about pharmacoeconomics in asthma in the published literature and what are the important aspects of the chronic disease of asthma which pose particular problems for pharmacoeconomic analysis?
3. How do the use and cost of asthma-related health resources measured in the same individual differ between the RCT and real life? What are the reasons for these differences?
4. How does having been chosen as a subject and having participated in an RCT impact on the measurement of the use and cost of asthma-related health resources?
5. What is the difference between the use and cost of asthma-related health resources measured in a group of clinical trial subjects in an RCT and those resources measured in real life in a group of subjects who have never participated in a trial?
6. What are the differences between the average use and costs of asthma-related health resources, estimated from the RCT and from real life, adjusted for age and gender to an index population: the Canadian asthmatic population?

7. In what ways does the construct validity of the RCT affect the capacity to generalise the measures of use and cost of health services from the RCT to real life?

The thesis is in 8 chapters, chapters 2 and 3 include articles reviewing the literature and chapters 5 and 6, in the form of articles, present the results of the experimental part of this thesis.

Chapter 2 addresses the first question, reviews the literature affecting the use of health services, then proposes and justifies a model for the exploration of the differences between the cost measure of the RCT and that of real life.

Chapter 3 is a critical review of the relevant literature of the disease of asthma and its treatment, focussing on iCST therapy. It incorporates a published article reviewing the literature on pharmacoeconomics in asthma, updates that review, and addresses the second question.

Chapter 4 sets forth the case study and the manner in which the thesis will address the balance of the questions using the case study.

Chapter 5 addresses the third question, exploring in particular the differences between the RCT and real life cost and use of asthma-related health services measured in the same individual.

Chapter 6 examines the effect of having been chosen as a subject on the cost and use of such services (question 4).

Chapter 7 presents the overall difference (question 5), synthesising the differences from the two previous chapters. It also tests the differences using another approach, adjusting the estimates of health services used to an index population, that of the Canadian asthmatic population (question 6).

Chapter 8 concludes the thesis and discusses the impact of the research on pharmacoeconomics in asthma. The last question is addressed by the entire thesis, but most fully in the conclusion.

The results of this study should increase our understanding of the RCT construct and how it may differentiate clinical trial from actual use conditions. Dealing with the outcome of use and cost of health services, it may tell us if we can differentiate the effect of the drug itself from the effect of the other factors which constitute the RCT construct. It may also contribute in general to guide the modelling process using the cost information gathered from the RCT, and with respect to the iCST treatment of moderate and severe asthma in particular. The research results may enable a more realistic translation of the clinical trial cost-efficacy data to cost-effectiveness data.

Chapter 2

Generalisation of costs measured in the clinical trial to the real life setting: review of theory and literature

Can the costs measured in a clinical trial be generalised to the real life setting? This chapter includes an article dealing with the concepts of the ability to generalise in the case of iCSTs for the treatment of asthma, and the development of a model for exploring the influence of the clinical trial setting on estimates of cost-effectiveness intended for decision-makers in the real life setting. Secondly the chapter explores the theoretical perspective developed in the social sciences literature discussing the validity of the design of the randomised experiment, of which the randomised clinical trial (RCT) is a classic example. We focus on the question of the generalisation of observations in the RCT to real life. This is followed by a discussion of the construct validity of the RCT as it applies specifically to the measurement of the use and cost of resources.

2.1 The problem outlined

Because of the demand for early information on the economic impact of drugs, the RCT carried on during the development of a medication, largely before it is marketed and sold to the general population, is often the source of the information used to estimate the economic impact of treatment (Rittenhouse, 1995). There are two main purposes of the trials which are conducted as part of the development of a medication: to demonstrate its

safety and to demonstrate its efficacy. The safety of the drug is first tested (Phase I) in a very small group of healthy subjects. Secondly, the efficacy (and further safety issues) are examined in a small group patients for whom the treatment is to be used (Phase II), and in larger sample sizes of patients (Phase III). Additional issues of safety and efficacy may also be addressed after the drug is approved for marketing (Phase IV) (Spilker, 1991).

It is generally accepted that the gold standard of research designs to demonstrate efficacy and safety is the RCT, because of the internal validity of the results. It is the results of the RCT that are most currently acceptable in the research, medical and regulatory communities. 'Faith in the randomised controlled trial is so firm among epidemiologists, clinical scientists and journals...that it may justly be described as a shibboleth, if not a religion' (Susser, 1995, p. 156).

The main purpose of the information gathered and evaluated during an RCT is to draw conclusions about the inherent properties of the pharmaceutical itself, to demonstrate that a causal link exists between the administration of the drug and certain clinical results. There is general agreement that it is a powerful design to answer causal questions when the conditions for comparing the test and control groups are sufficient to make that comparison valid (for examples see Campbell & Stanley, 1963; Cook & Campbell, 1979; Anonymous, 1994; O'Brien, 1994; Conrad & Conrad, 1994; Langley, 1995).

The problem is that the users of pharmacoeconomic information generally require an evaluation of a different type. Authors have put this in different ways. Schwartz & Lellouch (1967) talked about two different types of trials to compare treatments, the explanatory and the pragmatic. "...an explanatory trial is aimed at efficacy and understanding...a pragmatic trial is aimed at effectiveness and decision." (Diamond & Denton, 1993)

For questions about economic impact, we find ourselves no longer in the clinical sciences where the action of a drug in a human being is being evaluated, but in the field of social sciences where we seek information on the effect of a program on a population of human beings both in health-related terms and in terms of the use and cost of resources. Rather than a biomedical inference we are looking at the impact of a relatively complex treatment program. "When we study complex social programs, the understanding of treatment, its implementation, its observation, and its setting is important..." . (Conrad & Conrad, 1994, p.8). One should therefore question the value of the RCT for the study of this type of program, and many have.

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Cost-efficacy in pharmacoeconomics: a model exploring the influence of the clinical trial setting on estimates of cost-effectiveness

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Abstract

Estimates of the cost-efficacy of medication treatments resulting from clinical trials are limited by the conditions of the trials imposed by their protocols, which may differ widely from the conditions of real life. To aid in treatment decisions a clinician needs information applicable to the conditions of his or her practice and to the patients seen. To increase usefulness for resource allocation decisions, the information generated by clinical trials needs to be modelled taking account the constraints of real life and existing social structure. Using the example of patients with moderate to severe asthma treated with inhaled corticosteroids, this paper discusses the applicability of that information and the design of that model. The factors which distinguish clinical trial effect from clinical practice effect, and further from populational effect and the influence of these factors on the variation in health services utilization are examined.

Key words: asthma, drug treatment, model, cost-effectiveness

Introduction

Until the mid-1980s manufacturers of pharmaceuticals, health care professionals and government bodies were concerned mainly with the safety and efficacy of pharmaceuticals. However, toward the middle of the last decade, economic considerations increased in importance and became the object of intensive discussion, research and analysis.

The economic impact of pharmaceutical therapy has taken on importance to those making resource allocation decisions. The level of interest is dictated by several factors, including the regional economic climate, the unit or per treatment cost of the therapy, the number of potential or actual users, and the gravity (seriousness and duration) of the condition for which the patient is being treated. In times of constraint the economic impact of drugs commonly used (or potentially commonly used) to treat chronic conditions for a substantial portion of the population is therefore of relatively high interest because most or all of these factors are encountered. We have chosen to explore these issues using the example of asthma and its treatment by inhaled corticosteroid (iCST) therapy.

Types of effect measure

Essential for the evaluation of the economic impact of an iCST is its effect on the health of the persons using it, and indirectly on their consumption of resources.

Depending upon the design and setting of the study to evaluate the iCST, the measurement of the effect of the therapy will differ. Contandriopoulos et al. outlined four general types of effect measure which depend upon their general setting. (1) The first two effect measures are derived from experimental situations, the third and fourth from real life conditions. We have expanded upon the concept of types of effect by incorporating the different populations in which these effects are measured.

1) *Theoretical effect* is the measurement of the therapy in its isolated form outside of situational context. An example is the *in vitro* or bench effect of the active ingredient in an iCST on tissue samples when exposed to certain allergens. The effect is not measured in population terms.

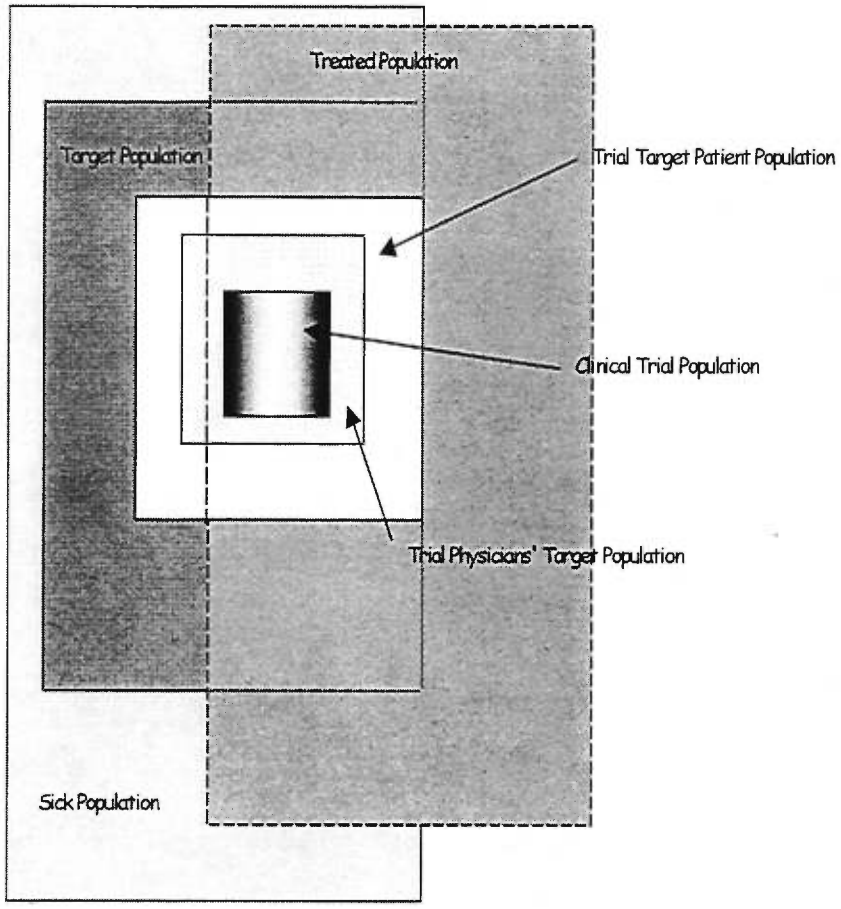
2) *Clinical trial effect* is the effect of the therapy in an experimental or quasi-experimental situation, under controlled conditions of administration and follow-up. It is measured in a population meeting a defined set of criteria for inclusion and exclusion, who have been selected according to those criteria, and who have given their consent to participate in an experimental situation.

3) *Clinical practice effect* is the measurement of the effect of the iCST in normal, uncontrolled, conditions. The use of the iCST is placed in the context of clinical practice, and is affected by the variation of the characteristics of the individuals involved in its use. It is measured in populations composed of patients who are seen, or who are likely to be seen in practice. It may also include some patients wrongly diagnosed as having asthma, and therefore receiving a treatment which normally would not be indicated.

4) *Populational effect* is the measurement of the effect of the iCST on a population level, with the variation of the characteristics of the individuals involved in its use as well as the variation in the accessibility to the therapy on a populational basis. It is measured in populations which include some patients who have no access to the medication. The population may also include patients who have asthma but have not been accurately diagnosed, and are therefore never seen as candidates for the treatment.

The characteristics of the population used to measure the *clinical practice* or *populational effect* have an influence on the measured effect of the iCST therapy and the generalisability of any conclusions which can or could be made about that effect. This can be further explored by looking at the manner in which these populations are recruited or drawn. Collet and Boissel (2) explored this concept and the first model in this article was developed from one of those used in their article. (Figure 1)

Figure 1 Populations in which to measure the effect of interventions



The *clinical practice effect* is measured in a well-defined group selected in a specified manner from the universe of individuals who have asthma.

The universe of asthma individuals we will term the Sick Population. Only a defined sub-group of the Sick Population having specific common characteristics will be considered appropriate for treatment by the iCST in question. This sub-group can be defined as the Target Population. As an example, they may consist of persons demonstrating a certain minimum level of bronchial inflammation, operationally defined as those showing minimum improvement of FEV1 after use of an inhaled bronchodilator.

A certain group of the Target Population will be defined by the inclusion and exclusion criteria of the clinical trial protocol as appropriate potential subjects for the trial itself. These criteria will be an age range, the absence of certain comorbidities, a limited smoking history, types of previous asthmatic treatment, numbers of crisis within a period preceding the trial enrolment, etc.. Those individuals of the Target Population which meet the criteria for enrolment will constitute the Trial Target Patient Population. Among the Trial Target Patient Population will be found the patients of the investigating physicians who are theoretically eligible for the trial: the Trial Physicians' Target Patient Population. And finally, those individuals who enter into the clinical trial as subjects, the Clinical Trial Population, will differ from the trial Physicians' Target

Patient Population because of elimination of the individuals refusing to participate or because of the selection/randomisation process.

The *population effect* is measured in a group chosen in a different fashion, generally use-based. Use-based populations are not derived by a process of "selection" from the Sick Population, but consist of all or some component of the group of individuals who are treated with the medication in question: the Treated Population. This includes a portion, but not all, of the Target Population, for reasons of access to the medication.

Limitations of clinical trial effect

The dilemma with which we are presented in the field of economic evaluation of interventions such as medications is that the studies which produce information about the economic impact of a medication will usually be conducted during the pre-marketing or early post-marketing stage of the drug approval process, at the same time as or in conjunction with the clinical trials carried on during Phases III and IV of the medication development process. In these phases of the development of a medication, the effect is usually measured by the classic randomised controlled and blinded (or not blinded) clinical trial which produces the *clinical trial effect* in the Clinical Trial Population. In consequence, the results of pharmacoeconomic studies at that level will be limited to conclusions about the effect under trial conditions of the drug studied, and the costs associated with that treatment as seen under

those controlled conditions and in a population corresponding to the Clinical Trial Population. The controlled conditions of the clinical trial yield results which are not necessarily applicable outside of the trial itself, and certainly not to normal conditions of use. (3-5)

In addition, information generated during the clinical trial may tell us little about the cost and the effect of treatment with the medication under normal conditions of use in other segments of the Target Population or in the Treated Population as a whole. The characteristics of the individuals comprising the populations may be quite different. There have been, for example, differences demonstrated between the indications suggested by drug use data under normal clinical conditions and the indications approved by the FDA. (6)

The factors which differentiate *populational effect* and *clinical trial effect* measures are inherent to the process of drug development. The main purpose of the information gathered and evaluated during a clinical trial of a medication is to draw conclusions about the properties of the pharmaceutical itself, to demonstrate that a causal link exists between the administration of the drug and certain results. It is for these reasons that the inclusion and exclusion criteria result in a Clinical Trial Population which may differ from the Target Population: comorbidities, age-related factors and non-adherent behaviours may exclude individuals, the trial investigators may not have certain types of patients, and refusers or patients which seldom see their physicians may not be selected.

For all these reasons data from clinical trials may be of limited use to clinicians; the effect of treatment in the Clinical Trial Population may be very different from that encountered in a professional practice. To aid in treatment decisions the clinician needs information from clinical trials which can be translated to his or her practice. For these purposes the effect needs to be defined under conditions of actual use, taking into account prescribing, distribution, dispensing, and utilization patterns. To increase usefulness for resource allocation decisions it has been suggested that information generated by clinical trials be incorporated into a model which takes into account these real life patterns and factors (7).

But how do we create that model? There are many factors which distinguish clinical trial effect from clinical practice effect from populational effect. This paper will focus on those factors.

These factors can be grouped into four types: 1) the circumstances and setting of the clinical trial, 2) the characteristics of the population, 3) the treating physicians' practice patterns, and 4) the social system factors which affect accessibility to and use of services. The latter three are the classical factors affecting use of health resources. (8-11)

The first category relates to the treatment the patient is given in the clinical trial in contrast to that given in real life. Treatment protocols in clinical trials

are (normally) rigid: the posology, dosage and mechanics of administration are fixed. Steps which are to be taken in case of treatment failure or adverse events are also usually well delineated. Persons are normally thought to be more adherent to dosing regimens under clinical trial than normal conditions, although average patient non-compliant use of aerosolised medications was seen in over 60% of the patient-days in one trial involving anti-asthma medication (12) and 15% of patients were seen to deliberately empty their inhalers in another (13). Adverse events are also associated with the clinical trial situation; a 19% overall incidence of placebo-caused adverse advents were reported in a retrospective review of double-blind studies. (14)

The second category includes those factors which define the relevant patient populations in terms of age, sex, demographic and socio-economic status, geographic proximity to health services, health status and attitudes toward health, illness, treatment and prevention. Comorbidities explained a significant part of patient cost for hospitalisations for acute and chronic bronchitis and asthma, even when the model included measures of disease-specific severity, physiology, and functional status. (15) Persons classed as accepting their asthma diagnosis were seen to incorporate prophylaxis (iCST) use into their daily routine, whereas those seen as denying their diagnosis were not taking their prophylaxis, although all had been prescribed them. (16)

The third category includes the characteristics of the health practitioners involved in the treatment, including their speciality, education, competence

and preferences. (17) There is considerable variation seen in the treatment of asthma by physicians. (18-23) Allergists have been seen to treat the disease more aggressively than internists, pediatricians or general practitioners, even controlling for disease severity. (18, 19) In particular, chest physicians in Holland were seen to use more inhaled steroids than general practitioners (20), allergists in the United States used corticosteroids (oral and inhaled) more than general practitioners or pediatricians, controlling for severity (of symptoms, hospitalisation and emergency room visits), (21) and replying to a questionnaire general practitioners and pediatricians recommended lower doses of inhaled corticosteroids than other physicians. (22) Younger physician age and the presence of a teaching physician in a practice group tends to be associated with more appropriate prophylaxis to bonchodilator ratio. (23)

The system structural category encompasses such factors as availability of treatments, and the financial structure of the system which will affect the choice and ease of access to such treatments. It is important to an analysis of populational effect, but also to clinical practice effect because individual patient behaviour can be influenced by the choices available and the cost of those choices. Although the conclusions in the literature about the importance of asthma patients' insurance status on the use of health services is mixed, (24) the costs of health services to the user has been seen to have an effect on their use, (25) and services which are free of user charges may be to a certain extent substituted for those which are costly or result in an expense incurred by the user. (9, 26, 27)

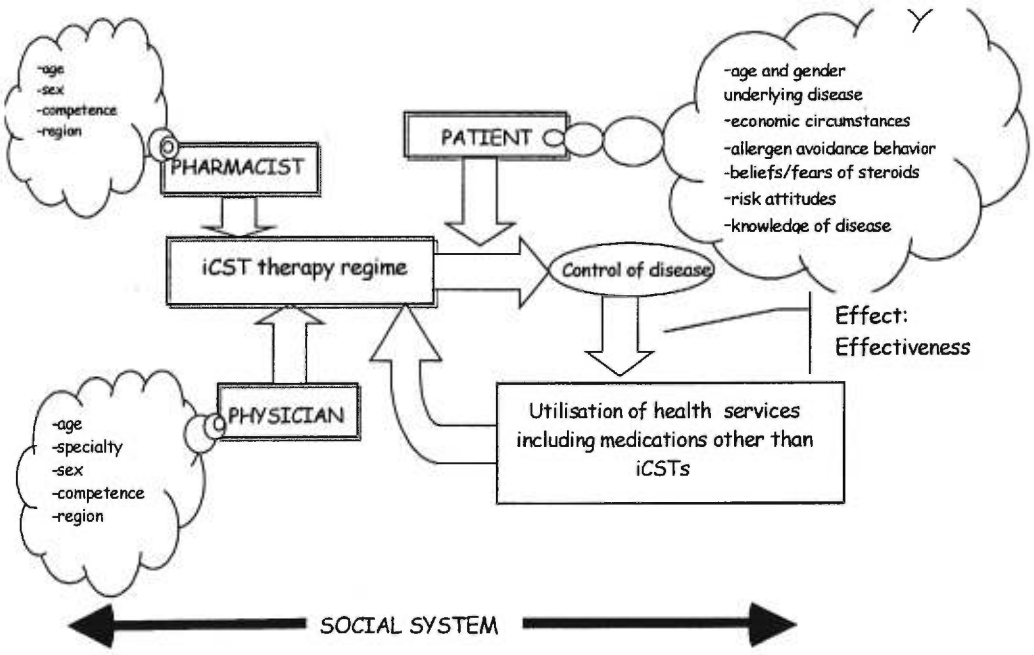
Development of the Model

With a medication group such as inhaled corticosteroids and a disease such as asthma, the premise is that, subject to the underlying seriousness of the disease, a "best possible" control of the disease can be established for any given patient. That best possible control is then subject to the factors of the system, patient and health professional which mean that the level of actual control may be less than that which could be considered "best possible." (Figure 2) Because corticosteroids are antiinflammatories which, when properly administered, reduce the reactivity of hyper-reactive airways in asthmatic patients, (28, 29) their correct use should result in the minimum utilization of alternative anti-inflammatory treatment such as oral steroids, and rescue-type health services, such as medications for symptomatic relief of wheezing (commonly beta-2 agonists), (30) emergency care visits and hospitalisations. These have been used as study end-points in inhaled steroid trials (31-33) and in evaluations of asthma education and monitoring programs. (34-39)

The effect of the corticosteroid medications therapy regime established for control of an individual's asthma will be subject to the influences of the patient (those which affect adherence to the appropriate medication regime), the ability of the physician to optimise the therapy (understanding of the patient, the severity of the disease, and the appropriate treatment), and the pharmacist, (ability to counsel the patient and encourage optimum medication

use). All these factors are subject to the social factors which mean that the patient has more or less easy access to health resources, and that certain resources are substituted for others which are for any reason less easily accessed. There is also a feedback loop built into the model, which ensures that the results (effect) of the medication regime can influence and change it. The model is not static but evolves over time, with the various factors having a changing level of influence on the influenced variable.

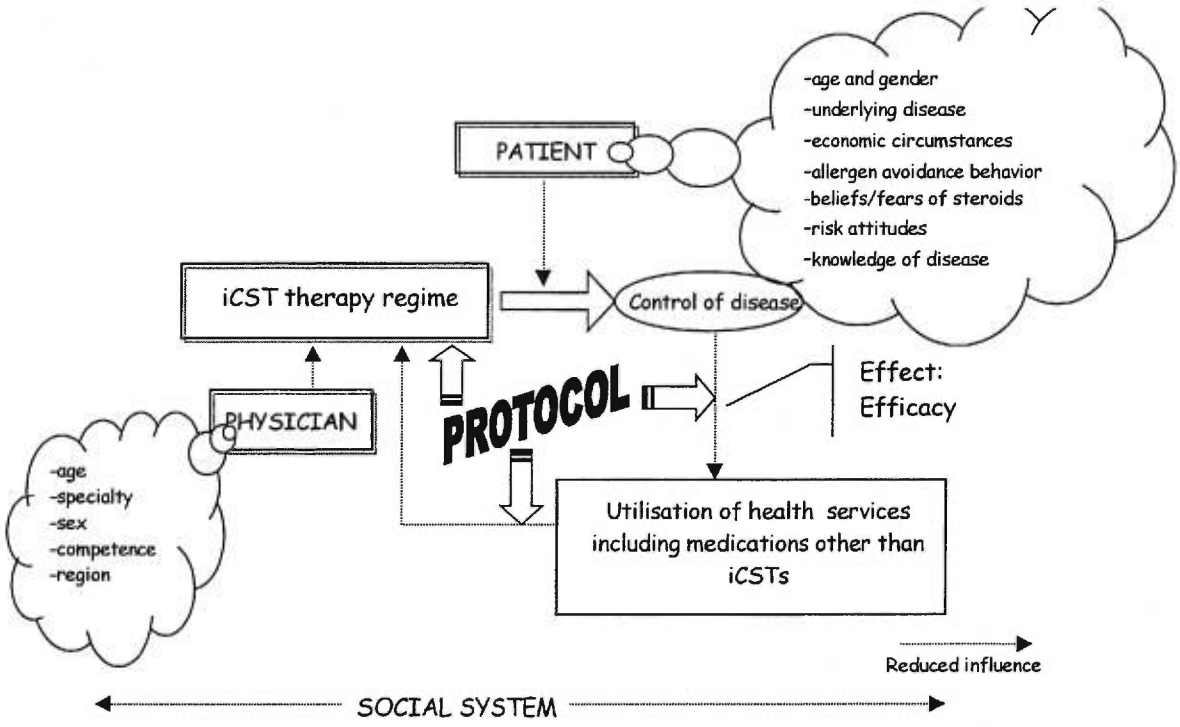
Figure 2 General Model: 3 classes of factors.



When the medication therapy is established for the patient during the course of a clinical trial in which patient is participating, there is significant

modification to this model, (Figure 3) and the factors specific to the treatment protocol of that trial dominate many of the other factors which under normal circumstances influence the use of health care services, and as a consequence the costs of those services used.

Figure 3 Model modified by the clinical trial setting



In the clinical trial, because the objective is to demonstrate the effect of the medication, efforts are made to reduce the opportunities for and range within which those factors which detract from "best possible" control can operate. The influence of individual physician and patient behavioural factors are reduced, although they can never be eliminated. The patient factors, for example influence the therapy regime less than the therapy regime influences the patient, for in the clinical trial the patient is chosen as eligible for the trial

according to a series of admission criteria which are more or less restrictive. In the area of compliance the patient factors continue to operate, but often at a less important level, because obviously non-compliant patients are often eliminated early on in the admission or lead-in period of a clinical trial, even if the analysis has been done on an intention-to-treat basis. And the physician factors play a less important role as well, because again the protocol defines the therapy regime, and often defines as well the utilization of other health services, including other medications, diagnostic tests and care in the event of treatment failure. Physicians with teaching responsibilities are more likely to be investigators in clinical trials than those without affiliations to the University-Tertiary care hospital complex.

Conclusion

The extent to which the protocol will modify and diminish the effect of physician, patient and social system factors on the use of services and the associated costs of iCST treatment for asthma are not well understood. In addition, if the characteristics of the Clinical Trial Population treated with iCSTs for asthma differs considerably from the characteristics of the Target Population, the control of the disease and thus the effect of the treatment and the utilization of health services and the costs associated should also differ.

REFERENCES (Numbered references for the article only. The remainder are found in the References section near the end of the volume.)

1. Contandriopoulos AP, Champagne F, et al. (1992). L'Évaluation dans le domaine de la santé: concepts et méthodes. L'évaluation en matière de santé: des concepts à la pratique, Lille.

2. Collet JP and Boissel JP (1991). Sick population--treated population: the need for a better definition. The VALIDATA Group. European Journal of Clinical Pharmacology **41**(4): 267-271.

3. Feinstein AR (1988). Problems, pitfalls, and opportunities in long-term randomised trials. Drug Research and Drug Development in the 21st Century, Bayer, AG Centenary Symposium.

4. Susser M (1995). Editorial: The tribulations of trials--intervention in communities. American Journal of Public Health **85**(2): 156-158.

5. Fayers PM and Hand DJ. (1977) Viewpoint : Generalisation from phase III clinical trials : survival, quality of life, and health economics. Lancet **350** : 1025-1027.

6. Mak H., Johnston P et al. (1982). Prevalence of asthma and health service utilization of asthmatic children in an inner city. Journal of Allergy & Clinical Immunology **70**(5): 367-372.

7. Rittenhouse BE and O'Brien BJ (1996) Threats to the validity of pharmacoeconomic analyses based on clinical trial data. Ch. 26 of Spilker, B., Quality of Life and Pharmacoeconomics in Clinical Trials, Second Edition. Lippincott-Raven Publishers, Philadelphia.

8. Anderson R and Newman JF (1973). Societal and individual determinants of medical care utilisation in the United States. Milbank Memorial Fund Quarterly **51**: 95-124.

9. Donabedian A (1976). Benefits in Medical Care Programs. Cambridge, Harvard University Press.

10. Contandriopoulos A-P (1994). Réformer le système de santé: une utopie pour sortir d'un statu quo impossible. Ruptures **1**(1): 8-26.

11. Béland F (1994). Introduire la durée dans la conception et la mesure de l'utiisation des services médicaux. Ruptures **1**(1): 28-44.

12. Mawhinney H, Spector SL et al. (1991). Compliance in clinical trials of two nonbronchodilator, antiasthma medications. Annals of Allergy **66**(4): 294-299.

13. Rand C S, Wise RA et al. (1992). Metered-dose inhaler adherence in a clinical trial [see comments]. American Review of Respiratory Disease **146**(6): 1559-1564.

14. Rosenzweig P, Brohier S and Zipfel A. (1996) Data on placebo in healthy volunteers : impact of experimental conditions on safety, and on laboratory and physiological variables during phase I trials. Therapie **51**(4) : 356-357.

15. Shwartz M, Iezzoni LI, et al. (1996) The importance of comorbidities in explaining differences in patient costs. Medical Care **34**(8) : 767-782.

16. Adams S, Pill R and Jones A. (1977) Medication, chronic illness and identity: the perspective of people with asthma. Social Science & Medicine **45**(2): 189-201.

17. Blais R (1993). Variations in surgical rates in Quebec: Does access to teaching hospitals make a difference?. Canadian Medical Association Journal **148**(10): 1729-1736.

18. Freund DA, Stein J et al. (1989). Specialty differences in the treatment of asthma. Journal of Allergy & Clinical Immunology **84**(3): 401-406.

19. Weiss KB and Budetti P (1993). Examining issues in health care delivery for asthma. Background and workshop overview. Medical Care ;**31**(3 Suppl):MS9-19.

20. van Schayck CP, van Weel C, et al. Treatment of patients with airflow obstruction by general practitioners and chest physicians. Scandinavian Journal of Primary Health Care 1989;**7**(3):137-142.

21. Engel W, Freund DA, et al. (1988). The treatment of patients with asthma by specialists and generalists. Medical Care **27**: 306-312.

22. Hodgkin JE (1986). United States audit of asthma therapy. Chest;**90**(5 Suppl.):62S-66S.

23. Sturdy P, Jaish J et al. (1995) Characteristics of general practices that prescribe appropriately for asthma. BMJ **311** : 1547-1548.

24. Sumner B and Lurie N. (1993). Financial payment systems and asthma care. Medical Care **31**(3 Suppl): MS74-81.

25. Nolan B (1993). Economic incentives, health status and health services utilisation. Journal of Health Economics **12**: 151-169.

26. Soumerai SB, Ross-Degnan D, et al. (1993). A critical analysis of studies of state drug reimbursement policies: research in need of a discipline. The Milbank Quarterly;**71**(2):217-252.

27. Soumerai SB, McLaughlin TJ, et al. (1994). Effects of limiting medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. New England Journal of Medicine **331**(10): 650-655.

28. Hargreave F, Dolovich J and Newhouse M (1990). The assessment and treatment of asthma: A conference report. J Allergy Clin Immunol;**85**:1098-1111.

29. Anonymous (1992). International Consensus Report on the Diagnosis and Management of Asthma. Clin Exper Allergy **22**: Supp 1.

30. Kaliner M. (1993). How the current understanding of the pathophysiology of asthma influences our approach to therapy. J Allergy Clin Immunol **92**: 144-147.

31. Tarlo SM, Broder I et al. (1988) Six-month double-blind, controll trial of high dose, concentrated beclomethasone dipropionate in the treatment of severe chronic asthma. Chest **93**(5): 998-1002.

32. Groot CA, Lammers JW et al. (1992) Effect of inhaled beclomethasone and nedocromil sodium on bronchial hyperresponsiveness to histamine and distilled water. European Respiratory Journal **5**(9): 1075-1082.

33. Tinkelman DG, Reed CE et al. (1993) Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics **92**(1): 64-77.

34. Mayo PH, Richman J et al. (1990) Results of a program to reduce admissions for adult asthma. Annals of Internal Medicine 112: 864-871.

35. Bolton MB, Tilley BC et al. (1991) The cost and effectiveness of an education program for adults who have asthma. Journal of General Internal Medicine **6**(5): 401-407.

36. Trautner C, Richter B et al. (1993) Cost-effectiveness of a structured treatment and teaching programme on asthma. European Respiratory Journal 6(10): 1485-1491.

37. Anonymous. (1994) Intergrated care for asthma: a clinical, social, and economic evaluation. Grampian Asthma Study of Integrated Care (GRASSIC). BMJ **308**(6928): 559-564.

38. Greineder DK, Loane KC and Parks P. (1995) Reduction in resource utilization by an asthma outreach program. Archives of Pediatrics & Adolescent Medicine **149**(4): 415-420.

Pauley TR, Magee MJ and Cury JD. (1995) Pharmacist-managed, physician-directed asthma management program reduces emergency department vists. Annals of Pharmacotherapy **29**(1): 5-9.

2.2 Experimental validity

Social science research theoreticians have developed other paradigms for discussing the usefulness of, and difficulties associated with, different research designs which attempt to show a valid causal inference from a treatment to an effect. Although there has been some debate concerning the types of validity, (for example see Hammersley 1991, Swanborn 1993 and Hammersley 1993), the approach developed over the years by Cook,

Campbell and associates seems to be well accepted (Campbell & Stanley, 1963, Cook & Campbell, 1979, Campbell, 1986). However, the approach to the ability to generalise the results of a study as defined by Cronbach (1982) and adapted by Conrad & Conrad (1994), appears to be logical and useful. It is a blend of these two approaches I will outline and apply in this discussion.

2.2.1 Types of validity

Although the terminology and the classification have varied with different authors and over time, validity can acceptably be viewed as three main types: statistical, internal and external (or construct) validity. Statistical conclusion validity deals with the ability to presume covariation of the variables of treatment and effect given a specific level of acceptable risk of error and the variances of the measurements (Cook & Campbell, 1979). The second type, internal validity, which Campbell later (1986) choose to call, certainly not for reasons of ease of use, 'local molar causal validity', deals with the ability to infer (until disproven) that the relationship between the variables tested and measured is causal, and that the absence of a relationship implies absence of a cause (Cook & Campbell, 1979). Campbell (1986) is not alone to point out that these are the types of validity that the basic sciences (including biomedical) emphasise. Researchers in those fields structure and limit their problems and testing situations with these validities in mind. These first two types of validity deal with the testing situation itself, without much reference to the outside world. By design, this type of research tries to isolate as far as possible the intervention from its context.

External (construct) validity, which deals with how the inferences drawn from the experiment can be related to the world outside, has been subdivided into three types. They are termed construct validity of causes (the treatment), construct validity of effects (the outcomes measured), and the construct validity of the generalisation of the theory of the relationship of the variables to other persons, settings and times, which implies knowledge (based on theory) of those persons, settings and times to which the relationship is to be generalised (Campbell, 1986).

Cronbach (1987) views the generalisability of the relationship as a question of external validity, and does not separate construct and external validity. His approach has been restated by Conrad and Conrad (1994): "External validity is simply the construct validity of the results of the study sample (utoS) generalized to the study population (UTOS), which is then generalized to other populations (*UTOS). 'External' construct validity also concerns whether the sample of units (u), treatments (t), observations (o), and Setting (S) accurately match or represent the population of Units (U), Treatments (T), Observations (O), and Setting (S), and other populations of *U, *T, *O, and *S."

2.2.2 Threats to construct validity (generalisability) of the RCT

The RCT, like most experiments in the 'hard' (as opposed to social) sciences is generally designed to emphasise statistical conclusion validity and internal

validity. I will not discuss those further because my interest in this thesis is in the area of construct validity.

The problem of the ability to generalise the results (construct validity) of the RCT to the non-experimental situation has long been known. Cook and Campbell (1979) point out that the use of the placebo in the RCT is to promote the construct validity of the treatment, and not for internal validity. The placebo effect is the improvement seen in a subject receiving an inert, non-active substance as a treatment. The improvement measured in the subject treated with the inert substance comes simply from being treated. Therefore, it is the difference between the two groups which reflects the 'true' effect of the medication being tested. This example highlights just one of the problems for pharmacoeconomic evaluation in the clinical trial setting. When we are measuring the use in health resources of the subjects in the clinical trial, we are measuring the results of the treatment, together with the placebo effect of being treated. Are we not in addition measuring the results of the treatment effect of the subject participating in a clinical trial? How do we separate those trial treatment effects from the rest? Can we differentiate the effect of the drug itself from the other factors which constitute the RCT construct?

Conrad and Conrad (1994) point out that the classic texts on the threats to validity tend to emphasise statistical conclusion validity and internal validity, and that a focus on internal validity in a study design (such as the RCT) leaves

open a series of threats to construct validity. The traditional RCT has not concentrated on the construct validity of the treatment which was measured, with the exception as noted above of the inclusion of placebo, and the later addition of blinding subjects and providers to the different treatments. Several authors have pointed the RCT's emphasis on internal validity, at the expense of external validity (Rittenhouse & O'Brien, 1996; Simon et al., 1995; D'Agostino & Kwan, 1995; Susser, 1995; Langley, 1995; Bloom & Fendrick, 1996; Cunningham et al., 1995)

The construct validity threats to RCTs (as developed originally by Campbell and others) have been categorised into 4 groups: those addressing the subjects (units), the treatments, the observations, and the settings (Conrad & Conrad, 1994). Although the list is more exhaustive, I will present some of the major threats under each of the categories, then go on to discuss, employing that terminology, the problems certain threats could pose for the measurement of use and costs of resources in RCTs.

2.2.2.1 Construct validity of the unit or subject (Are the subjects of the trial and their behaviour representative of real life patients?)

The subjects selected (unit of analysis) could be unlike the unit construct of interest, due to a high or selective rate of target subjects refusing to participate, due to uneven loss to follow-up in the different treatment groups, or due to subjects in one group objecting to their assignment.

The subjects could react to the experiment, behaving in different ways. They could behave as if they were in a study situation, that behaviour being different than normal (non-study) behaviour. The subjects could react to the group assignment in a competitive manner by compensating for the less desirable conditions, or in a defeatist manner by feeling (or behaving) worse, because of the less desirable conditions. Finally, there may be a reaction of anger or a feeling of injustice because of the random allocation to one or another treatment, or because of a perceived loss of the freedom or the right to make choices.

2.2.2.2 Construct validity of the treatment (Do the treatment protocol and the provider represent real life?)

Campbell (1986) called this the construct validity of causes, or the problem of generalising from the treatment used in the study to other treatments. Cronbach (1982) points out that this factor is not usually addressed in the classic RTC, because identification of the cause "...is not part of the claim for internal validity." (p. 130) "The experiment tests simple theory, that is, *A* causes *B*. Because the construct represented by *A* need not be clearly defined, experiments have generally been inadequate in their ability to specify the complexity and instability of constructs in social settings." (Conrad & Conrad, 1994, p. 17) Therefore, there is often a lack of a theoretical framework and conceptual analysis of the treatment in the research. The treatment is presented as whole, and the components and the relationships of those components are not understood.

The validity of the inferences drawn from the study could be threatened because only one example of the treatment was studied, and either the other possible examples were not known. The treatment as understood and interpreted could have been misdescribed as representing just a portion or a few elements of the entire treatment package. Often in the case of medical treatments, the treatment package includes not only the treatment, but its delivery by the provider.

Because of the need for control, the treatment protocol is often highly standardised. "Sometimes protocols do not reflect reality; they may not even reflect a desired reality, as RCTs do not operate with the same goals and constraints as the actual practice of medicine (the standard of care in the RCT may be beyond that appropriate from an economic or health care point of view in order to ensure the safety of participants—and their recruitment; the protocol-induced elements in a trial may well exceed the goal of even ideal practice)." (Rittenhouse, 1997, p. 332)

The individuals delivering the treatment could also affect the construct validity of the treatment because they were chosen for their special expertise and ability to effectively implement the treatment program. Another possible problem associated with the treatment standardisation demanded could result in the opposite reaction of the providers, who disagree with the 'script' or protocol delineated.

There could also be a reaction by the providers to the deemed 'clinically inappropriate' method of randomisation, although this is generally accounted for by the blinding procedure in the RCT of drug treatments. Because of the threat of contamination caused by increasing availability, over the period of the trial, of the scarce resources which form part of the program, the researchers could attempt to protect the control groups from these natural changes. The treatment tested could also represent an 'idealised' program, or, in contrast, the treatment tested could still be in the development stage and could therefor differ from that which may be ultimately used. If more than one treatment is being tested, there could be interactions between (among) those treatments.

2.2.2.3 Construct validity of the observation (Are the effects measured representative of real life effects?)

This is what Campbell called the construct validity of effects, or the problem of generalising from the outcome measures used in the study to other effect measures. (Campbell, 1986) Although most RCTs measure more than one effect, they still do not use all the possible relevant outcomes.

2.2.2.4 Construct validity of the setting (Is the social structure representative of real life?)

The context of the experiment, in terms of place (geographical), economic situation, political influences, and social forces may vary widely from other potential contexts. The setting may be changed by the study itself. Certainly

in the case of RCTs of drug treatments, the ultimate purpose of the study may be to change physician prescribing and patient consumption patterns, having an effect on background treatment patterns. The problem of timing is also extremely important. "An experiment may take two years to design, approve, and fund, three years to implement, a year to analyse, and another year to publish. This is a seven-year information lag." (Conrad & Conrad, 1994, p. 21) A lot can change in that time period, including the alternative treatments commonly used and the price structure of the health care system which could affect the cost of different alternative treatments to the patient.

2.3 Construct validity and the clinical trial measure of use and cost of health-related resources: introduction

An RCT, given certain design components, will generally allow inferences to be drawn with respect to the treatment *A* on the measured effect *B*. As noted above, the addition of placebo allows for a certain level of construct validity of the drug treatment, because the control group receives nonetheless a 'medication' and a level of follow-up.

Blinding of the study, both to subjects and to providers, counters the threats to certain aspects of the construct validity of the unit and the treatment. For example the subjects, resting ignorant of their assignment, would not compensate for the less desirable conditions, nor feel or behave worse because of the less desirable conditions (compromising the construct validity of the unit). Likewise, the providers, again ignorant of the assignment, would

not change the treatment modality for similar reasons (compromising the construct validity of the treatment).

However effective these measures are for decreasing threats to the external validity of the drug treatment itself, when the effect on use and cost of health services is considered, these research devices may in fact decrease the external validity of the measurements. The health services outcome measured by the RCT is that delivered by a mixture of the drug treatment, the clinical trial protocol, and their interaction. Every additional device which is incorporated in the RCT to improve drug treatment construct validity may in fact threaten the construct validity as it applies to health services use.

There are a number of additional threats to external (construct) validity, particularly when contemplating information useful for economic evaluations. This is because the construct of the unit, the setting, and the treatment in the RCT are often not representative of the constructs to which the users of economic information wish to apply the inferences drawn from the RCT. Even blinding poses special problems for the impact of different therapies on the use of resources when there are differences in administration or in acceptability, because blinding masks the effect of these differences (Simon et al., 1995). For example, the number of times per day a treatment is administered, or the administration of a drug by injection or by mouth will certainly affect acceptability.

Economic evaluations are generally geared to those individuals or bodies who make resource allocation decisions on a population level (Bloom & Fendrick, 1996). The inferences drawn from the limited constructs employed in the RCT, those constructs designed to augment internal and statistical conclusion validity, are couched in terms of those constructs. Those terms and those constructs are not necessarily applicable outside of the trial itself, and certainly not to normal conditions of use (Feinstein, 1988; Susser, 1995). In the words of Conrad and Conrad (1994) it is doubtful that "...the sample of units (u), treatments (t), observations (o), and Setting (S) accurately match or represent the population of Units (U), Treatments (T), Observations (O), and Setting (S), and other populations of *U, *T, *O, and *S..." which are the populations to which we want to apply the inferences of the RCT.

The pharmacoeconomic literature generally puts this problem of construct validity in terms of inferences about efficacy (the inferences using the constructs of the RCT) in contrast to inferences about effectiveness (the inferences using constructs of the populations in real life). Diamond & Denton (1993, p. 455) expressed the situation succinctly: "...the diffusion of technology from the investigational laboratory to clinical practice is fuelled more by the promise of performance than by performance itself. The drug, device or procedure must first have utility among a group of patients in an ideal setting (efficacy), but it must also have utility for the individual patient in a realistic clinical setting (effectiveness)."

2.4 Aspects of construct validity affecting the generalisability of resources use measured in the RCT

The constructs employed in the clinical trial differ from real life in various ways. A model for visualising these difference was developed in the previous section. The specific ways in which those differences will affect the measured use of health services in the RCT as contrasted to real life are further explored in this section.

2.4.1 Construct validity of the subject (How do the subjects in the RCT differ from those in real life?)

The previous section has pointed out that selection of subjects for the RCT does not necessarily represent the population which will be found in real life. This limits inference from the RCT to real life. Our question specifically is, what are the aspects of the real life construct of the subject which differentiate him or her from the RCT subject and which will affect the inferences which can be drawn about use of health resources and their cost?

The subjects in the clinical trial are most likely to be more homogenous in their potential response to the medications tested than would be the population in general (Simon et al, 1995). This is deliberate in the RCT: homogeneity reduces the variation in response to treatment within each of the treatment groups, therefore a smaller sample size is needed to show variation between the treatment groups, than if the within group variation were great.

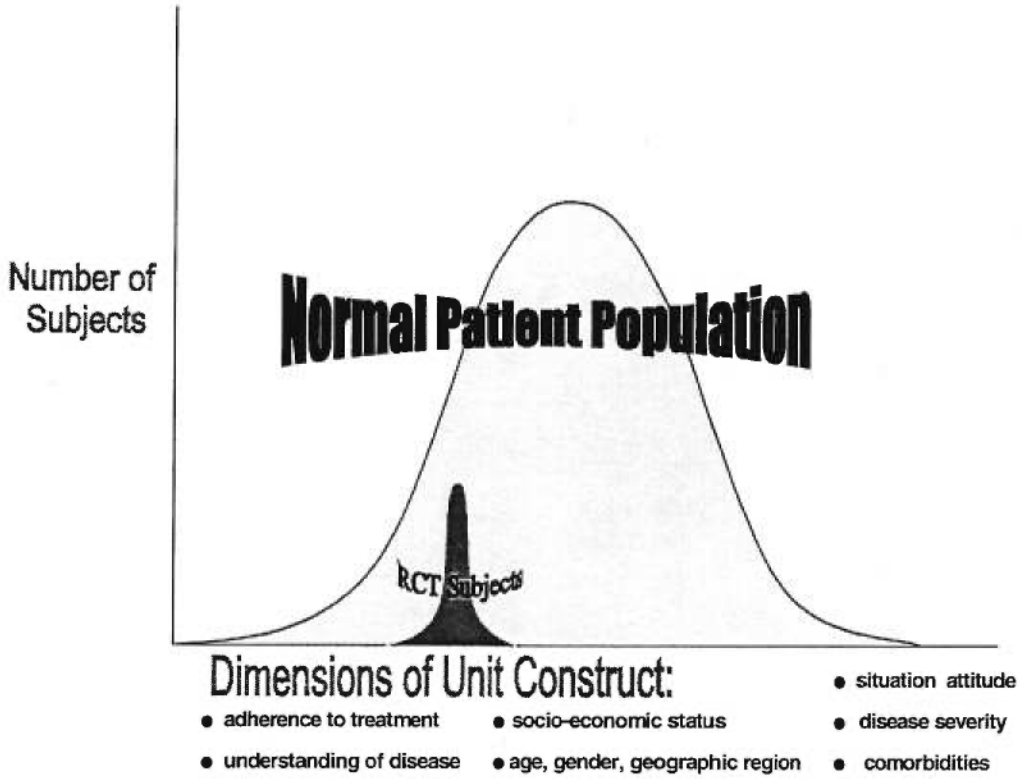
One of the reasons that a new medication is assumed to decline in average clinical effectiveness over time, is that physicians will generally start prescribing in subjects they think will have the best response, and then gradually enlarge the scope of type of subject over time, to include the less 'ideal' candidate. "Because additional patients introduce new variables (e.g., non-compliance), the overall or average clinical effectiveness of the product may decline" (Langley, 1995).

If the variables describing the subject have a significant influence on the use of services, differences in these variables between the RCT subjects and the real life subjects should affect the use of resources. Epidemiological research which investigated the linkage between drug exposure and outcomes of concern (such as adverse effects) have pointed out the importance of the variation in such patient characteristics (Leufkens & Urquhart, 1994). We developed the following illustration for this thesis inspired by their work.

Although not specific to asthma, patient characteristic variables seen to significantly influence the use of the services of general practitioners included age, sex, urban/rural residence, income and illness levels (Nolan, 1993) and overall use of health care services have been seen to be highly associated with age (Roos et al., 1989). Hospitalisation rates for asthma have shown to vary with age, sex, and geographic region (Weiss & Budetti, 1993; Laurier et al., 1994). The environment has long been accepted as influencing the prevalence and severity of the disease (Hendrick, 1989), and measured

asthma prevalence is higher in urban than in rural areas (Gergen & Weiss, 1990).

Figure 4 Subject construct differences: normal patient population and RCT subjects and the distribution of characteristics affecting use of health resources



Socio-economic status has an effect on both hospital admission rate and length of stay, poverty is associated with higher levels of both, although this information was not specific to asthma (Sumner & Lurie, 1993). Part of the

difference has been attributed to the substitution of hospital services (free of charge) for ambulatory services for which user fees were charged. Economic status has also been associated with behaviours which reduce asthma triggers (Denson-Lino et al., 1993). In the US, the economically disadvantaged are seen to have a higher prevalence of asthma (Evans III et al., 1987) but use primary care at a lower rate. In France, although similar rates of bronchial hyperreactivity were seen across income groups, economically disadvantaged groups reported greater severity of symptoms, and in these lower income groups there was a much lower use of treatment for crises and maintenance (Taytard & Touron, 1992).

Insurance status is also a factor influencing the use of services; having insurance coverage has been associated with higher use of services (Newhouse et al., 1981), and the rate of physician visits in children of poor and medically uninsured families was seen to be 33% lower than those with insurance (Weiss et al., 1992).

Patients vary in their use of health services not only because of the nature of their disease, their regional and socio-economic differences, but because of their overall health state, their cultural influences, and their personal attitudes gained from various professional and non-professional sources. The effect of the type of factors in which we are interested for the purposes of unit construct validity are those which are associated with, or which influence, compliance with prescribed medication regimens, and health behaviours associated with disease control.

Perception of health state was seen as highly correlated with use of services in a primary care setting (Connelly et al., 1989) and with the use of prophylactic medication in asthma (Adams et al., 1997). Personal habits, most particularly the use of tobacco, influence the disease (Mao et al., 1987; Barter & Campbell, 1976). This could be an aspect of economic status, as the use of tobacco is also inversely related to socio-economic status (Émond et al., 1988).

Compliance with medication therapy has been viewed as a particular problem in asthma (Taytard, 1992; Wilson, 1993), and especially with corticosteroid use (Fauroux et al., 1992), but is difficult to measure (Horn, 1992). A review of the literature of compliance in asthma indicated a typical non-compliance rate ranging from 30% to 70% (Bender et al, 1997). As discussed previously, problems with medication compliance should reflect on the use of health resources other than those medications.

Compliance behaviour enters not only into the construct of the unit, but is also implicated in problems of the construct validity of the treatment. As applied to the subjects, certainly individuals demonstrating good compliance are more likely to be enrolled in a trial than those which do not, but the actual manner in which the medication is taken (or not taken) will also define the treatment which is being analysed in the RCT. Because of this, trial subjects would also normally have a smaller range of compliance levels than would be seen in real

life. If there were a large number of very non-compliant individuals in the study, the variation in treatment response would be larger than with a group that contains only relatively treatment-compliant individuals.

In contrast, however, is the suggestion that there could be an increased treatment effect seen in real life because the subject can choose his or her own treatment, and a synergy could exist between that choice and the outcome (Rittenhouse & O'Brien, 1996).

The factors leading to poor compliance with medication therapy are relatively poorly understood, in part as the techniques used to measure compliance are highly variable (Cochrane, 1992). Compliance has been seen to be better in older, female asthmatics and those with more symptoms (Laird et al., 1994). In children with asthma, increased knowledge of the disease was associated with better asthma management when the level of knowledge was relatively low (Rubin et al., 1989) Knowledge of the disease and its treatment may be not sufficient to change behaviour, because the subject needs to be motivated and supported (Deenen & Klip, 1993).

The attitude toward medications and faith in the health professional could also be of particular importance. The perception of corticosteroids as threatening is associated with poor compliance, and the perception of threat was seen as inversely related both to knowledge of asthma and the strength of a supportive relationship with a key figure (a person considered close) (Woller et al., 1993).

The case of asthma treatment with iCSTs would be a good example of a medication associated with adherence problems. "Adherence is further undermined in the presence of chronic illness requiring prolonged treatment, where the prescribed medications are used prophylactically, and where the consequences of cessation of treatment are delayed." (Bender et al., 1997, p. 179)

The problem of loss to follow-up in the RCT may pose problems for the collection of economic data as well, as the data collection ends when the subject leaves the trial (Rittenhouse & O'Brien, 1996). There are two potential problems, particularly if the reason for the subject dropping out is not known. The individual may leave the trial because he or she feels better (the subjects responding best to the treatment may be lost), or because they are having trouble with the treatment (the subjects responding most poorly to the treatment may be lost) (Simon et al., 1995). In either case, a class of subjects with particular characteristics of resource use would be missed. Even an intention-to-treat design cannot completely compensate for this problem, as the use of resources must be hypothesised for the subjects who are lost to follow-up.

Lastly, the subjects may not be the same as they would be in real life, partly because they are reacting to the study situation itself (situation attitude), and behaving in a manner which is specific to the study. They could be compensating, positively or negatively, for the study situation, trying to be

'better' or 'worse' depending on their reaction to the conditions of the RCT. The positive effect of the RCT is the traditional 'Hawthorne effect'.[1] In another part, they could behave differently because they are learning from the trial situation to better control their disease and its treatment.

2.4.2 Construct validity of the treatment (How does the treatment and the way it is delivered differ from that in real life?)

It is perhaps in this area that the threats to construct validity of the RCT are the least understood. The treatment during the RCT is generally very strictly defined and rigid, the influence of the protocol is extremely important. Even so, the construct of what the treatment is deemed to be in the RCT may not always be what has in fact occurred.

To illustrate a common threat to treatment construct validity, the variation in the dose allowed by the protocol may be less than would be seen in real life, again reducing the variation in the response to treatment.

A complicated treatment requiring considerable monitoring would likely perform better under trial conditions, where intense monitoring is part of the protocol. In contrast, a more simple treatment regimen would likely fare better in real life, where follow-up is less important (Simon et al., 1995). The trial

[1] There was a study conducted in the Hawthorne Works of the Western Electric Company, intended to measure the effect of lighting levels on the productivity of the workforce. The results of the study showed a positive impact of all the lighting levels because the subjects were reacting to the additional attention they were receiving as part of an experiment. (Roethlisberger et al., 1961)

situation may also result in problems being picked up more quickly than in normal clinical practice, because the trial subject undergoes regular tests (Rittenhouse & O'Brien, 1996).

As mentioned by the theoreticians, the treatment construct includes the providers, which may be an important element of what is being measured by the RCT. And the literature with respect to the influence of provider characteristics shows a relationship to their patients use of health services. For example physician characteristics, including age, sex, speciality and clinical experience, influence their patients' utilization of health services in general (Eisenberg, 1985; Lockyer, 1992; Maheux et al., 1990). In respiratory disease including asthma, variations in professional practice may be associated with uncertainty of diagnosis, severity of illness and treatment (Weiss & Budetti, 1993). Again in respiratory disease, specialists and generalists have been seen to treat patients differently (Freund et al., 1989; Weiss & Budetti, 1993; Engel et al., 1988; Hodgkin, 1986; Vollmer et al., 1997).

The treatment construct of any given RCT would certainly almost always be characterised as only one of a plethora of possible treatments. As a rule, the research protocols which delineate the treatment of individuals enrolled as subjects in clinical trials set forth a standard schedule of treatment, including the medication dose. The element of rigidity in the quantity administered in the trial protocol is among the factors which are important to demonstrate the

characteristics of the medication. Similar consistent patterns of dosage are not likely to be seen under the conditions of normal use (Coyle & Lee, 1998). Other treatment variables which will be rigidly fixed under the protocol will be things such as the physician visits which form part of the research process itself, and often a set procedure in case of the deterioration of the health of the patient.

However, even the clinical trial treatment construct does not guarantee perfect adherence. The treatment construct will be affected by compliance in the selected subjects, even though they are generally pre-screened for good adherence to their medication regimen. Although there has not been a great deal of investigation into the reflection of the treatment construct measured in the RCT with the treatment construct defined in the protocol and thus assumed to be that which is measured, there are a several studies which cast some doubt on the assumption the two constructs are identical.

For example, the percentage of patients compliant to recommended asthma therapy (within 10% of the quantity of the prescriptions purchased as a percentage of those prescribed) has been measured at 40% after 5 weeks (Chmelik & Doughty, 1994). Lower rates of compliance (purchase of asthma medications prescribed) have been seen for iCSTs (54%) than for oral theophylline (79%) (Kelloway et al., 1994). When reported compliance rates were checked with a microprocessor monitoring device, a vast difference in reported versus measured use was seen (73% reported use of 3 times per

day, only 15% actually used the inhaler 2.5 or more times per day). This was also different than use which could be checked by weighing of inhalers, because some members of the study group were seen to deliberately empty inhalers (14% showed use of 100 times or more during a period of 3 hours) (Rand et al., 1992). One study showed such poor compliance that only 6 patients of 34 could be used to draw valid conclusions about the efficacy of the tested drugs (Mawhinney et al., 1991).

2.4.3 Construct validity of the observation (How do the outcomes measured in the RCT differ from those in real life?)

The focus of outcome measurement in the RCT is specific to the treatment and the trial situation. In contrast, in real life it would be part of the ongoing physician-patient relationship, which may have an impact on the use of resources which may not be directly related to the specific treatment. "This separation from patients' usual health care is especially problematic when evaluating the cost-effectiveness of newer, more expensive therapies." (Simon et al., 1995). An indirect effect on other health care resources, whether a decrease or an increase, would probably go undetected in the RCT.

"Trials often employ measurements for outcomes that are more detailed, invasive or frequent than is customary in usual care" (Rittenhouse & O'Brien, 1996). In asthma care, for example, the treatment may change in the RCT due to changes in measured lung function, whereas a physician in clinical practice may change treatment in response to reported symptoms.

2.4.4 Construct validity of the setting (How does the social structure of the trial differ from that in real life?)

The construct of the setting of the RCT is certainly only one of many possible settings in 'real life'. The social structure affecting the availability and the use of services in the community setting will normally be eliminated from the RCT. This should have a particular importance on the estimates of the use of health services measured in the RCT setting when compared to that of real life, because the use of these services are influenced by their availability. The services we are talking about in asthma treatment are also those which are affected (substituted for) by the level of use of other services. Therefore, the ease with which a patient has access to a given treatment among a series of appropriate alternatives will influence the frequency of its use.

Some examples of the logic of this substitution effect has been seen in the literature. Geographical differences will affect use of services. Asthmatic children living in rural areas were found in the US to have fewer physician contacts than their urban counterparts, but to have received more prescription products per provider contact (Bosco et al., 1993).

Availability or ease of access to services is not only geographic access, but financial access. Although not specific to asthma, the level of costs of health services to the user has been seen to have an effect on their use (Keeler et al., 1985; Newhouse et al., 1987; Nolan, 1993; Newhouse et al., 1981); services which are free of user charges may be to a certain extent substituted

for those which are costly or result in an expense incurred by the user (Donabedian, 1976; Soumerai et al., 1993; Soumerai et al., 1994). For two other chronic diseases, hypertension and diabetes, the method of physician reimbursement (capitation or fee-for-service) was not seen to have an effect on prescribing (Coffey et al., 1995). However, there is a suggestion that fee-for-service physician care would be associated with more services to asthma patients than capitation, because this has been seen in other areas (Sumner & Lurie, 1993). This would likely affect diagnosis (as the subjects would be seen more often), quantity of tests, the level of care during crises, and hospitalisation.

In Quebec, higher mortality rates (populational) were associated with asthma in 1979 in the far north regions of Kativik and Cri, which could be associated with the difficulties of access to health services for reasons of lower availability and physical distance, but also with the depressed socio-economic status of those regions (Boulet et al., 1989).

Medications play a particularly important role in the treatment of asthma. Regular use of iCSTs has been associated with a lower risk of asthma hospitalisation (Blais et al., 1998; Gerdtham et al, 1996). Therefore the access of the patient to reimbursement for medications should have an important influence on the utilisation of health services (Sumner & Lurie, 1993). This probably operates to affect the proportion of prescriptions received which are taken to the pharmacy to be filled, because an increase in

patient copayments was seen to have no effect on the payment for and pick up of anti-asthma prescriptions once they were presented to the pharmacist (Watt et al., 1992). This study does not look at the effect on prescribed medications, nor can it tell us if there is a different effect on new vs. renewed prescriptions, as the measure was of prescriptions presented to pharmacists.

The construct validity of the typical RCT of iCSTs for asthma with respect to setting is certainly, according to these indications, highly problematic. And, as mentioned earlier, the construct validity of setting is often difficult to separate from that of treatment in the area of drug trials. The subject generally has ready access to physician or professional nursing care, which forms part of the normal follow up of the protocol. These services are not only relatively easy to access (regular appointments made in advance, rapid access to services in case of problems) but they are thorough. The consultation time of these visits may be longer than for normal care. Affordability is not an issue in Canada for most physician visits, but certainly is an issue with respect to medication. Most RCT subjects would pay for at least a percentage of their medications outside the trial setting.

2.5 Capacity to generalise the measurement of the use of resources and their cost in the clinical trial setting: previous examples

'Generalisation always turns out to involve extrapolation into a realm not represented by one's sample. Such extrapolation is made by assuming one knows the relevant laws' (Campbell & Stanley, 1963, p. 17). But do we know

the relevant laws in the case of the measurement of the use and cost of health services? The discussion above raises a number of questions about the ability to generalise measures from the trial to the normal setting.

We found no articles exploring the construct validity of the RCT in asthma. However, one study examining Health-related quality of life (QOL) in AIDs patients looked at this dilemma, measuring the QOL in two groups of subjects, those in clinical trials and those not. They found significant QOL differences, even controlling for demographic (gender, age, race, insurance status, education) and clinical (severity[2], mode of transmission, CD4 count) differences (Cunningham et al., 1995). The average trial subject scores were all significantly higher (raw or adjusted) than were those of the non-trial subjects. The authors acknowledged the limitations of their study, particularly the fact that the non-trial subjects had been selected for symptoms which would be associated with lower QOL. However, adjusting for the symptoms, and comparing the non-trial group to a subset of the trial group with more symptoms did not change the direction or significance of the results. The authors concluded that there may be unidentified variables, and because these were (or could not be) known from the data gathered in their study, they raised doubts about construct validity, noting in particular (without using that terminology) the threat to unit construct validity.

[2] Severity was calculated using a score resulting from the addition of the use (1) or non-use (0) of 14 medications and the presence (1) or absence (0) of 17 symptoms over the prior 4 weeks.

2.6 Capacity to generalise the measurement of the use of resources and their cost in the clinical trial setting: hypotheses

The discussion leads to our preliminary hypotheses concerning the threats to construct validity posed by the RCT as it applies to the ability to generalise the use and cost of health services measured in the trial.

It is probable that the subjects in the trial have a smaller range of compliance behaviours (are more homogeneous), and the subjects are participating in a clinical trial and behave differently than they would otherwise (construct validity of the subject (unit). The providers of the treatment in the RCT are more qualified than the providers of similar treatments in real life and the treatment in the trial represents a fixed single example of the possible range of treatments in real life (construct validity of the treatment). The medications tested in the clinical trial cost the subjects nothing and the access to professional care is easier and more comprehensive than in real life (construct validity of the setting). Therefore:

Preliminary Hypothesis. The use of health services in the RCT will be less variable than that in real life.

It is also probable that the conditions of the RCT which improve the internal and statistical validity of the drug treatment contribute to the difficulties of construct validity of the RCT as they apply to the measures of use and cost of

health services. Therefore the outcome effect of the RCT as measured by the use and cost of health services is a result of the drug treatment, the other factors which constitute the RCT construct, and their interaction.

We propose to examine the construct validity issue using the example of the RCT in which subjects are treated with inhaled corticosteroids for asthma. We will then explore the generalisability of RCT measures of the use and cost of asthma-related health resources. The following chapter looks at asthma and the problems particular to pharmacoeconomics that a chronic disease such as asthma represents. The preliminary hypotheses will be further refined with respect to the case study proposed, and restated in Chapter 4.

Chapter 3

Asthma

This chapter discusses certain aspects of the disease of asthma: its prevalence, its economic impact, and the drug therapy used to treat it, with an emphasis on iCSTs. The chapter incorporates a published article reviewing the literature on the pharmacoeconomics of asthma, and concludes with an update of this review.

3.1 Asthma prevalence and burden of illness

Asthma is a common disease of both adults and children, and the population prevalence and incidence are generally agreed to be increasing (Health Canada, 1999; European Community Respiratory Health Survey, 1996). The self-reported prevalence of asthma 'diagnosed by a health professional' in Canadians aged 15 and older from the 1994 National Population Health Survey was 6.1% (Health Canada, 1996), up from a self-reported prevalence of 2.3% in 1978 (Manfreda et al., 1989). Due to the difficulties associated with the definition of asthma for epidemiological study purposes (Weiss & Budetti, 1993), including the problems in confirming the diagnosis by objective measurements such as the assessment of airway responsiveness (Sears, 1997), prevalence found varies considerably from one study to another and has been seen (in various populations) from less than 1% to over 13%. Asthma has consequences measurable in terms of mortality, morbidity and use of health resources.

The age-standardised mortality rate (1.5 deaths per 100,000 in 1995) has been declining in the 1990s, although it had risen during the 70s and 80s (Health Canada, 1999).

However, the true impact of the disease is difficult to measure for a number of reasons. The diagnosis of asthma can be problematic as there are no biological markers of the disease and diagnosis in general clinical practice is generally based on clinical judgement. It may be difficult to distinguish clinically between asthma and other chronic obstructive lung disease (Weiss & Budetti, 1993). Generally, diagnosis is made on the basis of a variety of symptoms such as whistling respiration, breathlessness, chest constriction, cough and expectorations, and when and why they appear, but the accuracy of the diagnosis can be reinforced if objective assessments of airway calibre and responsiveness are available and if these symptoms improve with the administration of anti-asthma medications (Malo et al., 1991). Failure to recognise asthma results in overuse of medications such as antibiotics to treat what is wrongly diagnosed as an infection. It also leads to under-treatment of the disease, which has been seen associated with higher hospital use (Mellis et al., 1993).

The consequences of the disease and the impact on the normal functioning reflected by the quality of life of the patient will vary considerably with the severity of the disease, the characteristics of the patient and the treatment received, entailing a considerable variation in health services utilisation. One

type of consequence often used as a morbidity indication because of its relative availability is that of asthma hospitalisations.

There was an increase in the rate of hospitalisation for asthma seen over the course of the 1980s, which reached 227 per thousand inhabitants in 1988 (Wilkins & Mao, 1993), but a slight decline appears to have occurred in the 1990s (Health Canada, 1999). The factors responsible for the earlier increase, in addition to the possible increase in the severity and prevalence of the disease, could be a change in the frequency of diagnosis, an increased tendency for physicians to hospitalise their asthmatic patients, or an increased average number of hospital visits per patient (Wilkins & Mao, 1993). Although often used as an indicator, hospitalisations do not reflect a very good picture of the impact of asthma. The rate of hospitalisation is relatively low in patients with less severe to mild asthma, making this indicator of limited usefulness except in the case of very severe, uncontrolled disease. Moreover, many patients visit the emergency room for treatment without being admitted to the hospital.

Several studies have examined the economic impact of asthma (McKinnon et al, 1996; Barnes et al., 1998; Krahn et al., 1996; Mellis et al., 1993; Sansonetti et al., 1989; Smith, 1997). The results of these studies vary for many reasons, including differing ways of determining the prevalence of the disease, use of different types of costs, and measuring costs in different ways.

A short sidebar is necessary with respect to the definitions of types of costs measured in economic evaluations. This topic is covered more fully in the following sections. In most of the literature on economic evaluation, costs have been divided into 3 major categories : direct, indirect and intangible.[1] Direct costs are generally those which are paid out-of-pocket, by the health care system, the insurance company or the patient and his or her support group. They include costs for medications, physician services, hospital services and transport. Indirect costs are those costs to the society such as loss of time from work or loss of productivity from early death (Drummond et al., 1986). Intangible costs would include pain and suffering.

Canada spent an estimated $306 million on the direct costs of asthma treatment in 1990 (Krahn et al., 1996); a recent publication estimated that direct costs of asthma (based on 1987 costs and expressed in 1994 dollars) in the United States were $5.1 billion (Smith et al., 1997). The annual cost to treat asthma in France was calculated relative to the severity of the disease in terms of the cost of diagnosis, hospitalisation, physician follow-up and medication (Sansonetti et al., 1989). Several cost of illness studies of asthma in various countries were translated into 1990 US dollars and presented a range of cost per asthmatic patient per year from $326 in Australia to $1315 in

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[1]The second edition of the Drummond and collaborators text has recommended a different taxonomy for costs. They categorise the cost by sector, costs to the healthcare sector, costs to the patient and family, and costs to other sectors. Most of the articles reviewed were written and published prior to the publication of this text, however, it should influence the way costs are reported in the future.

Sweden, with Canada falling roughly in the middle at $826 (Barnes et al., 1998).

Indirect costs for the treatment of asthma in Canada were estimated at $200 to $243 million for 1990. These included disability costs of between $76 and $98 million, school absence costs of $55 to $70 million, and travelling and waiting time from $12 to $21 million (Krahn et al., 1996). Costs due to premature death were estimated by that study at $55 million.

Medications account for a large proportion of the direct cost of asthma treatment. Krahn and colleagues (1996) estimated a 1990 cost of $124 million, which was the largest component and an estimated 41% of total direct costs ($306 million). This underlines the importance of drug therapy in asthma in Canada. Other components of the direct costs estimated by this study included hospital costs (28%), emergency visits (7%), physician services (15%), outpatient diagnostic tests (6%), devices (1%) and ambulance services (1%). This is different from an Australian study and two American studies that estimated prescribed medicines at, respectively, 61% (Mellis et al., 1991), 16% (Smith et al., 1997) and 29% (Weiss et al., 1992) of total direct costs for asthma. These widely differing results (from each other and from the Canadian study) illustrate the problems of estimating cost of illness using different methodologies and the importance of the structure of the health system in different locations. This is also different from diabetes, for

example, where the largest proportion of costs are for treating complications of the disease (Leese, 1992).

3.2 Pharmacotherapy in asthma

Asthma medication treatment for symptomatic relief and for prevention of inflammation is one of the 'four components of effective asthma management' set out in the recent guidelines for treatment of asthma developed by several national authorities, including the National Heart, Lung, and Blood Institute's (NHLBI) National Asthma Education Program (National Institutes of Health, 1997). As part of the therapy for long-term control, iCSTs are now considered 'the mainstay of therapy' (Barnes et al., 1998), although other anti-inflammatory preparations are available. The Canadian Thoracic Society has stated that iCSTs are the best agent for controlling the disease (Ernst et al., 1996). Numerous studies have shown them to be efficacious in reducing airway hyper-responsiveness and decreasing the need for other anti-asthmatic medications including bronchodilators (Kaliner, 1993). In the NHLBI guidelines, recommended treatment depends on the severity of the disease. Daily use of iCSTs is recommended in all moderate and severe persistent asthma, and in the mild persistent type it is recommended as one of the alternative anti-inflammatory treatments (other alternatives being cromolyn and newer anti-inflammatory preparations such as antileukotriene derivatives) (National Institutes of Health, 1997).

Use of anti-asthmatic medications is common. More than 3% of the prescriptions filled in US pharmacies in 1985 were for medications which are used to treat asthma (Bosco et al., 1987). In Australia, average utilisation of bronchodilators, measured in terms of defined daily dose (DDD), increased from 6.9 DDD per thousand inhabitants in 1975 to 25.0 in 1986 (Jenkins et al., 1990).

Various studies have reported different levels in the use of iCSTs, but the tendency is an increase in use over time. Use has been reported both in terms of proportion of total anti-asthma prescriptions and in terms of proportion of users. In Switzerland, evidence of use of iCSTs increased in a sample of asthmatic patient files from 33% in 1977 to 75% in 1987 (Bregenzer et al., 1990). In England, 35% of asthmatic patient files in general practice showed corticosteroid use (Horn et al., 1989). In Sweden and Denmark, iCSTs represented, respectively, 38% and 35%, of anti-asthma medication sales in cost terms (Larsson et al., 1993; Hallas & Hansen, 1993). However, measurement in cost terms is influenced by the high price of iCSTs in relation to that of bronchodilators. In a study of asthmatic Medicaid patients in the US, use of iCSTs in the mid-1980s increased with age from 0% in the group under 5 years of age to 9% in the group aged 30 to 44 (Gerstman et al., 1989).

In Canada, using a sample of prescription data gathered on an ongoing basis by a market research organisation, prescriptions for airway medications

increased 38% from 1985 to 1990 (Kesten et al., 1993). The same study found that prescriptions for iCSTs increased from 9% of all airway drug prescriptions in 1985 to 15% in 1990. The Kesten study also examined data from a sample of physicians (recording patients, diagnoses and prescriptions on 1 day per month), and found that of all patients diagnosed with asthma, the proportion having received an iCST rose from 4.8% in 1985 to 11% in 1990. In a study of anti-asthmatic medication users in Quebec over the period of one year (1990), 43% of those individuals aged 67 or over, and 37% of those receiving income security benefits used an iCST (Laurier et al., 1997).

3.3 Pharmacoeconomics in asthma

There is a growing interest in economic evaluation of medications to treat all chronic diseases, including asthma. Undoubtedly the increase in the use of the medications as discussed above has contributed to this interest. Economic evaluations of medications (pharmacoeconomic analyses) are not normally a regulatory requirement for any agency which is responsible for the pre-marketing approval of medications, as approval for marketing of products is still based upon the criteria of proven efficacy and safety. Thus, it is left to the agency(s) responsible for the financial support of the provision of drug therapy to take into consideration evidence of potential economic impact. Several jurisdictions, most notably Australia, now routinely examine economic effects of drug therapies as part of the administration of government-funded drug reimbursement programs. The closest example is the Province of

Ontario, but Quebec will also look at this information if submitted as part of an application for a provincial formulary listing.

An earlier published review of the English-language literature of the economic appraisal of asthma and/or chronic obstructive pulmonary disease care interventions found 20 articles published on this subject, none conducted in Canada (Rutten-van Mölken et al., 1992). Most of these dealt with health education programs, some with pulmonary rehabilitation programs, and some with delivery systems for bronchodilators, but none (at the time) with any pharmacotherapy. However, one study which had been published in Swedish had found that the use of high doses of iCSTs did reduce hospital stay, and showed the overall costs of health care diminished during the second and third year of treatment (Adelroth & Thompson, 1984). The study has certain limitations, being a pre-post study with no control group, and the fact that in English it is only in abstract form makes comment difficult. Additionally, the subjects were very severe asthmatics and use of an effective therapy should be associated with a relatively easily seen decrease in the use of healthcare resources. Since the Rutten-van Mölken review, we have found a number of studies published which associate lower costs with the use of iCSTs (Connet et al., 1993; Booth et al., 1996; Perera, 1995; Balkrishnan et al., 1998;). Other studies have shown an increase in overall costs associated with the use of iCSTs, partially offset by a decrease in health care costs other than the iCSTs (Rutten-van Mölken et al., 1993; Rutten-van Mölken et al., 1995).

In 1997, we published a review of the literature of pharmacoeconomics in asthma (see the section following). Since that time, several other studies have come to our attention. Certain concepts and definitions have since changed as well, with the publication of the second issue of *Methods for the Economic Evaluation of Health Care Programs* (Drummond et al., 1997) which is the main textbook in the field. Therefore, this review is followed by an update of the literature review, a discussion of these articles in the light of the recent developments, and a revised table which includes the additional articles.

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Pharmacoeconomics in Asthma: A Critical Overview[2]

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Abstract

Pharmacoeconomics has grown from the proliferation of new (costlier) medications and the limitation of new dollars to spend on them. There are five or six main types of pharmacoeconomic studies. Cost-evaluations describe the economic consequences of a treatment. Cost-consequence analyses list the costs and the effects of alternative treatments. Cost-minimisation analyses compare the costs of alternatives which are presumed of equal effect. Cost-effectiveness analyses compare the ratios of cost with effect of alternatives where the effect is measured in natural units. Cost-utility analyses measure the effect of alternatives in survival terms that are weighted by the utility or value of the health state associated with that survival. Cost-benefit analyses measure both cost and effect in dollar terms. A number of

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published studies are reviewed, and several issues in the conduct of pharmacoeconomic studies that are of particular pertinence to the economics of asthma drug treatments are discussed. These include the appropriateness of the effect measured, which should optimally be both meaningful to those deciding between treatments and allow for comparisons to treatments not included in the study. The comparators used for the evaluation of new treatments are most useful if they are likely to be replaced by the new treatment. Costs evaluated should reflect the impact of the treatment from the point of view of the society as a whole. As asthma can affect productivity in adult asthmatics and parents of children with the disease, inclusion of a measure of the indirect costs valuing this productivity loss is important. There are a few published studies in populations with varied characteristics and for longer periods, the majority is in shorter clinical trials with highly selected samples. The ability to generalise these results to real world populations and settings is arguable, particularly in a chronic disease that affects a large and varied population.

Keywords: asthma, costs and cost analysis, economics, drug treatment, evaluation, cost-effectiveness, cost-utility

What is Pharmacoeconomics?

Pharmacoeconomics can be seen as a subset of the larger field of economic evaluation of healthcare interventions, those which touch on some aspect of

pharmaceutical therapy, policy or practice. 'Pharmacoeconomics identifies, measures and compares the costs and the consequences of pharmaceutical products and services' (1).

The practice of pharmacoeconomics and the proliferation of pharmacoeconomic studies have developed as a response to two conflicting pressures: the increasing availability of, and demand for, new technologies in the form of new medications, which are usually costlier than the ones they are intended to replace, and the decreasing availability of new budget sources and increasing demand on current budget sources. (2) Most pharmacoeconomic analyses are conducted to evaluate new drugs or new therapies to determine how the health outcomes and the costs associated with these new therapies compare to those of existing therapies. The demand for these studies have in large part originated with the groups responsible for financing patient treatments (3).

Pharmacoeconomics evaluates alternatives by comparing their health outcome(s) with the resource expenditures required. It can lead to more efficient use of scare healthcare resources when comparing two or more interventions. It can help decision makers estimate which interventions give higher returns for the same cost, cost less for the same returns or give the highest returns for additional cost. It can estimate the overall impact of a new therapy in terms of the additional resources to be consumed and the additional health outcome returns.

Those who can benefit from the information provided by pharmacoeconomic analyses include anyone who needs to make an informed choice between alternatives that involve medications or pharmaceutical services: health professionals, patients, hospital or administrative formulary committees, health insurers, and public or private health program providers.

The published literature contains a number of studies reporting economic evaluations of medications or drug-delivery systems for asthma treatment, educational programs directed at improving patient self-care and methods of patient care. Reviews of the literature were published in 1992 (4, 5) and partial reviews in 1993 (6)and 1996 (7-9).

This article adds to these reviews by focussing on drugs and methods for administering drugs. It is not an exhaustive review of the published literature of pharmacoeconomic studies in asthma, although we have reviewed many of the articles (see Table 1 for a summary). Most notably we have not reviewed articles published on the cost of illness in asthma.

Types of pharmacoeconomic evaluations

There are five to seven main types of pharmacoeconomic evaluations, depending upon the taxonomy used by various authors. (1, 10-13) Full evaluations are those that look at both cost and health outcome, while partial

evaluations are concerned only with cost (the cost evaluation) or only with outcome (such as the clinical trial). This article discusses cost evaluation and the various types of full evaluations. What all full evaluations consider are the costs associated with the therapy or service measured in dollars and some measure of health outcome. What differentiates them is the units in which the outcomes of the therapy or service are measured.

A full pharmacoeconomic evaluation generally reports results both as a ratio of cost to outcome for each alternative in the analysis, and incrementally, where the difference in cost is expressed as the numerator, and the difference in outcome as the denominator (14).

The following is a brief description of each type, together with examples found in the published literature.

In a cost-evaluation the economic impact of the introduction of a treatment can be estimated, or the costs of two or more different treatments can be compared. No ratio is expressed, and no health outcomes are discussed. Cost evaluations of asthma drug therapies have been reported for inhaled steroid use in oral-steroid dependant adults(15), the inclusion of cromoglycate in asthma therapy (16), and treatment with albuterol (salbutamol) compared to orciprenaline (17). There have also been cost-evaluations of a drug delivery system: a change in policy of introduction of metered-dose inhalers for bronchodilator therapy in hospitalised patients (18, 19).

The costs to be included in a pharmacoeconomic evaluation can be broken down in to three categories: direct, indirect and intangible costs. Direct costs are those which can be seen to be directly incurred or paid by any of the individuals or institutions concerned by the treatment, and include costs to treat any side-effects. Indirect costs are generally defined as loss of productivity of the patient or his or her family or unpaid caregivers. Intangible costs have been considered to be the value of pain and suffering. This last category has generally not been considered in pharmacoeconomic analyses except as an outcome.

In a cost-consequence analysis there is no attempt made to express the results on a cost per unit of outcome basis. No ratio is expressed. Ideally, this type of study identifies and lists fully all the costs associated with the therapies or services studied, then lists all the outcomes of each with the estimated probabilities of occurrence of each outcome. Although a ratio of cost to satisfaction units was expressed, a study of the costs and effect of inhaled steroid use (beclomethasone or budesonide) in children, is essentially a cost-consequence study (20).

A cost-minimisation analysis looks only at the costs of the compared alternatives because an assumption is made that the consequences of the alternatives evaluated are the same. Therefore the outcome or denominator part of the ratio is deemed irrelevant and it is the numerators that are

compared. The assumption of identical or reasonably identical consequences can only be made in limited situations, and has not often been seen in pharmacoeconomics. This type of analysis can probably be justified in cases where there are two versions of the same drug, where different presentations of a drug are shown to have the same or almost the same clinical effect, or where there are 'me-too' types of drugs which have the same or almost the same clinical effect. This type of analysis has been used to evaluate drug delivery systems, namely comparing nebulizer with metered-dose inhalation of bronchodilators (21, 22).

The cost-effectiveness analysis is the most commonly seen of the pharmacoeconomic analyses. The results of this type of study are generally expressed as ratios of the cost of each alternative to its health outcome measured in natural health units, together with the incremental differences between the alternatives. The outcomes of the alternatives studied may be expressed in more than one type of unit, but each outcome requires a separate ratio and a separate comparison. This raises the issue of the most appropriate type of unit in any given evaluation.

The results of any cost-effectiveness evaluation are often restricted to the study comparisons. In order to 'export' those results to compare them to other therapies, a more general outcome, common to all therapies, is needed. In asthma, there may be a number of candidates for common outcomes appropriate to the disease and its treatment, such as average lung function

improvement (FEV_1, FVC, PEF), use of short-term bronchodilators, symptom-free days, or emergency department visits. Use of one or two of these in all cost-effectiveness analyses in asthma treatments would enable comparability between studies.

A number of cost-effectiveness analyses of asthma medications have been published recently, including bronchodilator therapy combined with beclomethasone and with ipratropium compared with bronchodilator therapy alone in adult asthmatic and COPD patients (23), bronchodilator and budesonide compared with bronchodilator alone in children (24, 25), two dose levels of budesonide (26), fluticasone compared with cromoglycate in children (27), oral salbutamol compared with placebo in bronchodilator users (28) and formoterol compared with salbutamol (29).

Considered by some authors to be a type of cost-effectiveness analysis, cost-utility analysis measures the outcome of therapies in a unit of measure intended to facilitate broad comparison. Most often used is the quality-adjusted life year (QALY). (For a discussion of other measures such as the HYE or healthy-years equivalents, and SAVE, or saved young life equivalents see [30].) The outcomes of the treatments are usually first expressed in survival terms (average years of life gained per subject) and then valued according to the utility of the health state associated with that survival.

There are several methods of assigning values to these heath states. All these measurement tools attempt to produce a value or utility weight that places the state of health on an interval scale of 0 to 1, where 1 represents perfect health and 0 (usually) represents death. This weight is then used to adjust years of survival producing the QALY.

Value or utility weights may be measured directly, by presenting the health state to subjects and estimating a value based on their evaluation, or indirectly by relating the health state to an already valued set of its components which are combined to express a relative utility. The former generally uses one of three tools for determining preference. The Standard Gamble (31) is an instrument which produces true utility weights by eliciting preferences under conditions of uncertainty. The other two tools both produce a value, and not a true utility weight. The Visual Analogue Scale asks the individual to place the health state to be valued on a linear scale between 0 (death) and 1 (perfect health) and the Time Trade-off instrument (32) asks the individual to choose an equivalent time in perfect health to a stated number of months or years in the health state to be evaluated.

Indirect measures of utility or value weights are determined using multi-attribute scales designed for this purpose. Examples are the Health Utilities Index (33), which provides utility weights, and the EuroQol (34, 35), which provides value weights. These measures break down overall health-related quality of life into various attributes or domains, such as pain, mobility, and

emotion, and create levels in each domain using descriptive statements. These levels are then combined to produce specific health states which can be assigned values. Many of these combinations have been assigned utility or value weights by population samples. A health state to be valued in a study can therefore be mapped with regard to these already valued combinations. Using the study subjects or the already determined combination weights the state can be given a utility or value.

Although there has been much interest in utility, it is fraught with measurement and validity questions (36). The authors are aware of no cost-utility study of asthma medications. Two studies formally used utilities measurement but neither measured costs. The first compared salmeterol to salbutamol and included a utility questionnaire among 3 other measures (37). The second compared four instruments including a utility instrument in asthmatic children (Juniper, 1996, unpublished presentation May 11, 1996 American Thoracic Society, New Orleans).

Cost benefit analysis (38) expresses the outcomes of the alternative treatments in dollars. If the outcome of importance is survival or years of life, the traditional approach has been to measure life-years as human capital. This measures the value of a human being as his or her economic productivity. Another way to put a dollar value on outputs have been to ask people, either directly or using a technique to control for their different levels of respective wealth, how much they would be prepared to pay for a specific

amelioration in a health state or improvement in quality of life, or conversely, how much they would be willing to pay to avoid a deterioration. The authors have not seen a cost benefit analysis for an asthma drug treatment.

In addition to taxonomy based on the type of analysis performed, studies can be classified according to their design. A pharmacoeconomic analysis can be based on a randomised clinical trial, or conducted in conjunction with such. In this case the collection of the data on health outcomes of the treatments and the utilisation and cost of health resources used by the different arms of the trial are generally carried out prospectively over the course of the trial. Retrospective study of use of resources and of effect among patients enrolled in a trial is also possible, using hospital, pharmacy, and physician services files. Modelisation is a different type of design. It often uses meta-analysis to synthesise information from different sources. To estimate resource use, the course of disease and treatment can be modelled using both primary and secondary information sources. If published secondary sources are unavailable, expert information can be sought from practitioners.

The estimated results of a pharmacoeconomic evaluation depend upon a number of inputs which are uncertain. For this reason, the results of any pharmacoeconomic analysis are normally submitted to a series of tests known as sensitivity analyses. The objectives of these sensitivity analyses are twofold: to determine which of the various estimated inputs threaten the robustness of the results, and to give a range of results. These analyses are

done varying the values of the tested inputs either singly or by varying the values of combinations of two or more simultaneously (39).

The following are examples of different types of analyses using different designs. As indicated above, we found no cost-utility or cost-benefit studies. There are examples of both prospective randomised clinical trials and retrospective studies, but no published modelisation studies.

Reported pharmacoeconomic studies of asthma treatments

Cost-evaluation, cost-consequence studies

Perera (20) studied a cohort of 86 children who had never used inhaled corticosteroids by following them for 1 year after they began using corticosteroids. Improvement after inhaled corticosteroid use was reported in several measured outcomes including school attendance, wheeziness, hospital admissions, acute severe attacks, and parental satisfaction with treatment. Costs (health service costs, costs incurred by parents for travel and indirect costs from productivity losses of the parents) were seen to decrease considerably after inhaled steroid treatment. The validity of these results could, however, be affected by problems associated with recall: the initial effect measures were taken retrospectively, as were both the before and after cost measures. The parents were asked to remember a 12-month period. Although certain events would be not subject to much recall error (hospitalisations and acute severe attacks if sufficient to warrant emergency

visits), many of the measured effects and costs would likely be recalled with questionable accuracy. The positive effect of close surveillance, intensive and continued education with respect to asthma control, and participation in a clinical trial also should not be underestimated in this study and are impossible to differentiate from the impact of the changed drug treatment.

Although the English-language report is limited, Adelroth and Thompson (15) described a before-and-after study of high-dose inhaled budesonide. They reported considerable reduction in the overall total costs of health services in 36 oral steroid dependent patients between the 2-year period preceding the study and the 2-year period after the study began. A difference was still present during the third year. The increase in outpatient visits (14%) was offset by a considerable decrease in in-patient treatment days (75%), resulting in a net average annual reduction in medical costs of 55%. The limited information available in the publication makes it difficult to comment on this study. However, it should be noted that the patients were very severe asthmatics who are likely to be high users of costly hospital care. It is in this group which an effective therapy will generate a decrease in use of healthcare resources more easily.

Ross and co-workers (16) conducted a retrospective review of medical files of a group of asthma patients in one practice. Patients were mostly children with level of asthma severity sufficient to have had at least one emergency treatment with adrenaline (epinephrine) during the year prior to referral and

regular daily use of anti-asthma medication. They were divided into two groups, those whose treatment regimens included cromoglycate and those whose regimens did not, and their use of medical services (anti-asthma medications, office visits, emergency room visits and hospitalisations) was followed prospectively and retrospectively for about 3 years. A comparison between the two groups was made, as well as a comparison of the number of emergency and hospital visits before and after the entry of the individual in the practice. The number and interval between office visits was similar for the two groups. Differences were seen in the number of emergency visits and hospital admissions with the cromoglycate group showing both a decrease from baseline and fewer visits than the other group over the study period. Medication costs were similar in both groups over the course of the study, but average daily cost showed a gradual decrease over the course of the study for the cromoglycate group, contrasting with a gradual increase for the other group. Total costs were lower for the cromoglycate group because of lower frequency of emergency and hospital visits. An annual difference of over $US1300 was estimated. The effect is seen in the reduction of emergency department and hospital resource use, and was measurable in this group of patients chosen on the basis of historical use of emergency services. The fact that the two groups were not randomised is the most important criticism of this study, even if at baseline, the clinical characteristics of the asthma symptoms of the two groups were similar. The non-cromoglycate group appeared to be older (the only adult subjects were found in this group, even

though the average age was 9.7) and were, according to the authors, not as sick.

Tierce et al (17) reported the results of a retrospective analysis of Medicaid data comparing patients using one of two β_2 adrenergics: orciprenaline (N=237) or salbutamol (N=1585). Patients were selected on the basis of having at least two asthma diagnoses recorded in the claims database, and having at least two prescriptions for the relevant bronchodilator, and none for any other β_2 adrenergics. Their average use of and cost of anti-asthma medications, physician visits and hospital visits were measured and compared. Although the cost of salbutamol use was higher than the cost of orciprenaline, the lower cost of other anti-asthma medications in the salbutamol group meant there was no significant difference between the medication costs of the two groups. The overall costs were lower in the salbutamol group due to the fewer number of physician visits, the lower hospitalisation rate and shorter length of stay. Total average cost per salbutamol user was US$370 less than per orciprenaline user. As in Ross et al (16), the main criticism of this study is that there is a possible difference in the characteristics of patients belonging to each group.

In a study of the cost impact of implementing a policy change from nebulizer administration of bronchodilators to metered-dose inhalers, Bowton et al (18) examined the program for a period of 7 months in a before-and-after study in

a tertiary care facility. For 3 months, the total monthly cost of delivery of this respiratory therapy was recorded, the change in policy was introduced in the fourth month, and the costs were evaluated for that and a subsequent 3 months. The program routinely substituted metered-dose inhaler for nebulizer orders unless the order was for no-substitution or the respiratory therapist felt the patient was unable to ensure adequate metered-dose inhaler use. Costs were measured both in patient charges and in costs of study drugs, equipment and therapist time, the last from time and motion studies. The program found that over 60% of the bronchodilator orders were by metered-dose inhaler in each of the last 3 months, at a cost saving to the institution of almost US$7000 per month (US$83 000 annually). The annualised saving to patients was almost US$400 000 based on charges. Cost differences were found mainly in therapist time, which although higher for the initial metered-dose inhaler patient administration session, fell to lower than nebulizer administration for subsequent treatments. However, the costs to implement the program (educating staff and deciding which patients should be changed) were not included. It is possible that continued education would be necessary to keep the metered-dose inhaler proportion at the study level after the end of the study period. Few institutions have implemented this policy, notwithstanding unanimous research findings supporting lower cost for comparative effect. This study also illustrates the vast difference between the use of charges and true costs for calculating economic effect.

Turner et al. (19) examined the costs of delivering bronchodilator therapy in a prospective observational study of adult patients who received this therapy in one hospital centre. Unlike the other studies of this type, there was no experimental design of a program or treatment implantation. The researchers measured the cost of administration of three types of bronchodilator therapy (nebulizer, metered-dose inhaler or both) in the patients to whom this therapy was administered over the course of the observation period, with no attempt to change the administration protocols. Over a period of 6 weeks, 95 adult patients were observed, the greatest proportion were treated with nebulizer alone (71%), 23% with both, and only 6% (N=6) with metered-dose inhaler. No attempt was made to measure effect. Costs of the therapies consisted of study drug and equipment costs and the cost of respiratory therapy and nursing care, but excluded overhead. Nursing care time was determined from time and motion studies. The study reported considerable variation in the costs to deliver treatments, particularly the cost of nebulizer, as there was a range of doses and combinations of salbutamol and ipratropium. The resulting cost differential for delivery of equivalent salbutamol doses indicates that metered-dose inhaler cost US$0.90 less per treatment than nebulizer did. The interpretation of these results is limited by the low number of metered-dose inhaler subjects studied, but could also be due to the staff being less familiar with a metered-dose inhaler routine and thus less efficient than if more treatments were administered. Among the factors which differentiate these results from those of similar studies is the very much shorter time for administration of nebulizer found in this study. In addition, nebulizer in this

study was seen to be administered more often by nursing staff who spent much less time supervising the administration; in the other studies respiratory therapists were responsible for nebulizer administration. An aspect which is never discussed in these studies is the potential post-study beneficial effect of metered-dose inhaler administration education on those patients who continue metered-dose inhaler therapy after their release.

Cost-minimisation studies

Two other studies examined the delivery of bronchodilators by metered-dose inhaler or nebulizer using the cost-minimisation approach as they measured effect as well as costs. Both studies found the effect of the alternatives to be similar and proceeded to compare the treatment costs.

Jasper et al. (21) randomised patients admitted to the pulmonary ward of a tertiary-care teaching hospital who were prescribed bronchodilator $ß_2$ adrenergic therapy. Thirty-four adults diagnosed with obstructive lung disease received orciprenaline by either metered-dose inhaler or nebulizer therapy. Costs were based on study drug and equipment costs, and the respiratory therapists' labour costs for nebulizer administration and the first instruction session for metered-dose inhaler delivery. The per-patient cost calculation was not explicit, but the cost savings estimated for replacing nebulizer by metered-dose inhaler in all eligible admissions was over US$250 000 per year. The differential is due mainly to the higher labour cost to administer nebulizer, based on 20 minutes per session. However, the study

did not include nursing labour time cost to deliver and pick up the metered-dose inhaler for each treatment. Metered-dose inhaler treatment did not include any supervision time for administration after the initial training session and did not measure any significant effect differences between the metered-dose inhaler and nebulizer treated subjects.

A similar study published in 1989 by Summer et al. (22) compared metered-dose inhaler terbutaline to nebulizer orciprenaline in patients admitted to a university-affiliated community hospital. Thirty-two adult patients with asthma or COPD receiving bronchodilator therapy were randomised to receive metered-dose inhaler or nebulizer. Effect was measured by lung function tests (FEV_1, FVC, and PEF) and length of hospital stay. Costs were patient charges and institution costs of study medications, equipment and estimated respiratory therapist time for each treatment multiplied by the number of treatments for each study arm. Metered-dose inhaler was seen to be significantly less effective than nebulizer in only one (baseline day 5 hour post treatment FEV_1/FVC) of the 24 effect measures between the two treatment arms, and was seen to perform better (six measures) or not differently than nebulizer in all others. The estimated costs were over US$600 to treat the 16 nebulizer patients compared to US$130 for the 16 metered-dose inhaler patients.

Cost-effectiveness studies

Sculpher and Buxton (29) estimated the difference in cost-effectiveness between formoterol and salbutamol use, in a sample of 145 asthmatics needing daily bronchodilator rescue therapy. The treatments were not seen to be significantly different according to two of the four effect measures used (number of episode-free days, EFD; number of adverse-event days, AED): formoterol use was associated with significantly fewer asthma attacks per week and lower average daily use of rescue salbutamol than salbutamol use. The costs of health services measured were limited to the study drug, rescue drug (salbutamol) and an estimated daily cost to treat adverse events. Although the difference in EFD was not statistically significant, the authors have calculated a cost-effectiveness ratio of cost per EFD. The limitations of the study with respect to lack of significance in effect was acknowledged, and the article was presented as an application of the measure of EFD in economic evaluations (rather than presenting the results of the comparison between the two medications). Interpretation of the results is difficult because of the lack of detail with respect to the use of health services that was measured, particularly insofar as adverse events are concerned. However, it is a good example of the results of a study in which neither therapy dominates the other: formoterol was seen to be more effective but also more costly than salbutamol. The article also illustrates well the use of sensitivity analyses, varying the definition of EFD and the average daily cost to treat adverse events. The analysis was conducted defining an EFD as a day without an

either an asthma or an adverse event, and using an alternative analysis which defined EFD as a day without an asthma event. In the first case, formoterol was seen to cost US$7.29 per additional EFD when compared to salbutamol, in the second US$5.67 per additional EFD. Increasing the cost per day of adverse event increased the incremental cost per EFD of formoterol.

Rutten-van Mölken et al. (25) studied 116 asthmatics between 7 and 16 years of age, over a 3-year period. The children were randomised to receive $ß_2$-agonist therapy plus placebo (B2), or $ß_2$-agonist therapy plus budesonide (B2+BUD). Effects of the therapies were measured by FEV_1 as percentage of predicted value, PD_{20}, the number of symptom-free days, and the number of school days missed. Information on the use and cost of health services for asthma were collected (study drugs, oral steroid rescue therapy, inhaled fenoterol rescue therapy, antibiotics, and other drugs such as mucolytics, antihistamines, theophyllines, homeopathic drugs, cough and cold medications, out-patient visits, tests and telephone contacts with a health professional not determined by the research protocol and hospitalisations). Indirect costs associated with loss of work (paid or unpaid) caused by school days missed were calculated for one parent, using the average hourly wage. Cost-effectiveness ratios were calculated excluding these indirect costs. B2+BUD was seen to be more effective than B2 on all measures. In the first year, difference in changes in percentage of predicted FEV_1 was 12% higher on average, and difference in PD_{20} was 1.53 doubling dose steps on

average. Over the course of the study, average yearly absence was 2 days lower in the B2+BUD group and there were 38 more symptom-free days on average per year. The conservative calculation of the cost differences between the two groups estimated B2+BUD to cost about f.200 (Dutch guilders) more than B2 in the first year, although a less conservative approach resulted in annual cost of BUD being f.190 less than B2. The conservative calculation estimated costs cumulatively for sequential 2-month periods based on the patients staying in the study, and the less-conservative calculation assumed that the drop-outs (there were more drop-outs in the placebo group) would have had the same average results in costs as they did before they dropped out. Incremental cost-effectiveness for the conservative approach found that B2+BUD cost f.175 per year per additional 10% increase in FEV_1, f.270 per additional doubling doses increase in PD_{20}, f.90 per additional day of school absence prevented, and f.10 per additional symptom-free day.

In another cost-effectiveness study published in 1995, Rutten-van Mölken et al. (23) compared the costs and effects of three therapies in adults with asthma and COPD over a period of 2.5 years. Two hundred seventy-four patients were randomised to receive bronchodilator (terbutaline) therapy with placebo, (TER) inhaled corticosteroid (beclomethasone–TER-BEC) or anticholinergic (ipratropium–TER-IPR). Effect measures were similar to those of the previous study, but instead of school absences, activity-restriction days (ARDs) were used, asking the subjects for those days on which normal (paid

or unpaid) work could not be performed due to their disease. Costs were the same as those in the previous study. To calculate an annual cost for those patients who dropped out prior to completion of the study (there was a high dropout rate in both the TER-BEC and TER-IPR groups) the costs incurred prior to dropout were annualised. In all effect measures (except ARDs where the difference did not reach significance), TER-BEC was seen to be significantly better than TER or TER-IPR, and there was no significant difference seen between TER and TER-IPR. Using the normal cost approach, total healthcare costs per patient-year were lowest in TER-BEC, and highest in TER. The estimated cost per year for TER-BEC was $US650, US$720 for TER-IPR, and US$730 for TER. Because of the wide range of some of these costs, (particularly hospitalisations) the researchers log-transformed the non-drug costs, and used a regression equation to predict costs by treatment standardising for differences in baseline treatment. Without that transformation there were estimated savings for TER-BEC, but the transformation resulted in an estimated US$200 additional annual cost for TER-BEC compared to TER. Because TER-IPR is more costly and no more effective than TER, it becomes dominated by TER and the incremental cost-analysis is therefore estimated for the additional effect and cost of TER-BEC only with respect to TER. TER-BEC was estimated to cost an additional US$5.35 per added SFD, and about US$200 per added 10% increase in FEV_1. There was a non-significant difference measured in ARDs, and we could conclude either the sample size was too small to show significance or the population studied was not ill enough to demonstrate a difference in this

variable (less than 50% in each group recorded one or more ARD). This study is a very good illustration of cost-effectiveness of asthma drug treatments. The study did use per diem charges instead of actual costs of hospitalisations; although preferable, actual costs are more difficult to determine.

The most recent publication reviewed compares the costs and effects of fluticasone to cromoglycate. In Booth et al. (27), 125 asthmatic children, aged 4–12 years, who had never received prophylactic inhalation therapy, were randomised to receive one of the two study drugs for 8 weeks. Effect was measured by proportion of patients successfully treated, measured during the final 3 weeks of the study and calculated in 4 different ways: no serious adverse effects combined with: (1) no daytime symptoms; (2) no night-time symptoms; (3) mean morning PEFR 90% of predicted; (4) mean evening PEFR 90% of predicted. Costs consisted of the costs for use of study drugs, rescue salbutamol and asthma-related hospitalisations (of which there were none). Fluticasone was seen to be more effective than cromoglycate on all effect measurements and at a lower cost. The cost to treat with fluticasone is both lower for the study drug and the cost of rescue medications used. The cost per treatment success is about £27 less for fluticasone for the 8-week period. The results remained robust to a sensitivity analysis which varied the definition of effect and the cost of relief medication. This study does not appear to have been analysed on an intention to-treat-basis, although the withdrawal rate was higher for the cromoglycate than the fluticasone arm.

The range of costs measured was very limited, and did not take into account the cost to treat adverse events, although again, the number of these appeared to be higher in the cromoglycate arm, which means the cost-effect ratio estimated may be conservative.

Critical Questions in Pharmacoeconomic analyses of Asthma Treatments

Outcome measure

Which outcome is the most appropriate for comparing asthma therapies in pharmacoeconomic studies? A mortality measure, which can be expressed in lives or years (saved), may be appropriate for treatments of acute asthma, or the very severe asthmatic, but most treatments for this type of chronic disease do not affect survival, particularly over the short-term.

Lung function tests are relatively easily measured, but their correlation to subjective patient health status has been disputed (40). Changes in FEV_1, expressed as a percentage change in predicted value, were used in the two Rutten-van Mölken studies. As this type of measure is used often in clinical trials of anti-asthma treatments, it may be one of the better outcomes used for comparison purposes. But other measures may serve to better reflect subjective patient well being or capacity to carry out normal activities, or the treatment effect on overall population health and well being.

Measures of effect which look at use of resources, such as the use of rescue bronchodilators, the number of visits to emergency departments or hospital days are meaningful because they reflect the impact of the treatment on the health status of the patient. They may also be used as cost rather than effect measures, depending upon the study design. However, their measurement may be accompanied by other difficulties: the use of rescue bronchodilators may be affected by patient compliance (i.e. they are acquired but not used) and reporting problems (used but not reported), or difficulties with drug administration techniques (used but not absorbed). Emergency department visits and hospital stays, although they are important consumers of resource dollars, are accounted for by relatively few patients, and require rather larger sample sizes to demonstrate differences in therapies.

If measured as an effect, the value of resource use rests not on their dollar value, but on what they mean in health terms. Resource use also serves as a component of the costs associated with treatments. In those circumstances the issue of double-counting occasionally arises. An example is seen in Rutten-van Mölken (25) when indirect costs, although collected, were properly not used as a cost component because one of the outcome measures was days of school absence, and it was those days which determined the indirect costs.

There is a general interest and an increase in use of the health-related quality of life as a health outcome, as measured by the various general

instruments (41), or those specific to asthma (40, 42). This type of measure demonstrates the effect of treatments in patient-oriented terms that reflect the impact of the disease and its amelioration on the life of the individual affected. The unit of measure is difficult, however, to translate into economic terms useful for decision-makers, particularly when comparing asthma treatments to treatments in other diseases. There are a variety of asthma-specific instruments used in studies, and cross-study comparisons can only be made when the same instruments are used. In particular, results of the discriminant ability of generic instruments have not been very promising in asthma treatment (37).

The choice of outcome measured in any particular study depends generally upon the purpose of the comparison and the use to which the end results are to be put. For purely efficacy purposes, lung function tests may be the most appropriate to show a measurable difference between two treatments explicitly. To aid clinical decision-making, outcomes which are patient, symptom or function oriented are preferable. For administrative decision-making, the outcomes must at least enable comparison with other treatments in an asthmatic population or allow a wider population comparison. This latter requires an outcome either in general patient-related survival or quality of life terms so that comparisons can be made between different groups of patients in the population for which the administration is responsible. Alternatively, outcomes must be translatable

into terms which affect health-resource utilisation to enable optimum use of resources for a given population.

Symptom-free days have been used in 3 studies of asthma drug treatments (23, 25, 29). It appears to be a measure that can be used in much asthma research. It would, however, be inappropriate for very severely diseased asthmatics (where there would be few or no symptom-free days). A similar concept is that of patients successfully treated (27), although there is no accepted common definition of 'successfully treated', and it is likely to be inappropriate for long studies or those involving very severe asthmatics.

A recommendation has been made to incorporate the symptom-free day measure in asthma studies to promote comparison (8). This, in addition to developing a gold-standard quality-of-life instrument would go far in promoting between-study comparisons for asthma treatments. It leaves unanswered, however, the question of comparability with other disease treatments.

Costs measured

The direct and indirect costs to be included in the analyses depend upon the perspective of the study. There are equity arguments for using the broadest perspective and measuring the costs from all society members equally. Guidelines and recommendations for pharmacoeconomic evaluations may recommend the study be conducted from society's point of

view (13, 43). The societal point of view includes all costs incurred to treat the patient, whether by the patient, his or her family, the health system, the insurer or the employer. It is because of the multiplicity of decision-makers and perspectives that the social perspective has been recommended in the Canadian guidelines for economic evaluation of drugs (13), as it forces the inclusion of the greatest number of cost items, and enables the widest possible comparability of the treatments studied.

Major items included are the costs of the evaluated drugs and their administration, costs of other drugs, hospital costs, physician visits, respiratory function and laboratory tests, pharmacy fees, travelling expenses for the patient and family, and some measure of time lost from work. The importance of the classes of each type of expenditure to the overall cost of asthma has been estimated in the various cost of illness studies which have been published (45-48). Medications to treat the disease have been seen to have a low overall per person cost but a high use rate and have been estimated to be the highest contributing factor to costs in Canada and in the UK. In contrast, hospital costs are the highest in the US (9, 45). Although used by a small proportion of patients, hospital care is associated with the highest unit cost. Therefore in any study, the cost of the few hospitalised patients will influence the overall average cost of any treatment. The wide variation in these costs can make the use of arithmetic means misleading, and the special analytic treatment of these

costs by log-transformation(48), as was done in Rutten-van Mölken (23), may be appropriate.

How are the costs of asthma differentiated from costs of other health problems? Normally the costs of all drugs to treat asthma should be considered in the measurement of direct costs in a pharmacoeconomic study. Most anti-asthma drugs are easily distinguishable. But should antibiotics and cold medicines be included or not? Certainly asthma exacerbations are sometimes interpreted as colds or flus. Costs for antibiotics and cold medicines were included in 1995 Rutten-van Mölken study (23). Although probably measurable in prospective trials, cold medications could be of particular difficulty in retrospective studies as they are often not prescribed and thus are not found in reimbursement program data banks, and would be subject to extreme recall problems in questionnaires.

Sometimes it is also difficult to determine whether resource use is asthma-related or not, particularly in retrospective studies of records. For example, a hospitalisation could be initially caused by a comorbidity, but prolonged because of the asthma complications. Diagnoses recorded by physicians for visits or consultations may be uncorrelated to the health problem which prompted the visit, or may represent only one of the several problems for which the patient was seen.

How are the costs of the time of the patient and caregivers to be valued? The time of caregiver relatives can be valued at the market cost of equivalent services (49). These were explicitly included in indirect cost measurement for child care in Rutten-van Mölken (25) even when incurred by a parent not working outside the home, and valued at the average hourly wage for the country. Unpaid time, such as leisure time, can be an important element. Most individuals are willing to forego a certain number of income-producing hours for leisure pursuits, and leisure hours occupied with an illness or treatment can be given a value consistent with that concept. None of the studies reviewed included a cost for leisure time. The debate over inclusion of these costs is ongoing.

Indirect costs are often extremely important topics for discussion in asthma treatments, first because of the controversy surrounding how they should be measured, and secondly because a large proportion of the asthmatic population is relatively young, healthy and economically productive. These costs have been estimated as an important part of the total cost of asthma in various cost-of-illness studies. For example, it was seen as almost 40% of the total cost of asthma in Canada, based on the rate of disability days from health surveys. The productivity loss for these days was estimated using average weekly earnings adjusted for labour-force participation for those employed outside the home, and for home-workers by using an estimate of their productivity-valued average earnings for those employed in domestic work (46). Asthma-caused illness was assumed to reduce the

productivity of the affected individual, and asthma exacerbation in children to affect their parents' ability to work. Absence from school was thus estimated at over 25% of indirect costs in Canada (46). The economic impact of longer-term absences or permanent removal from the workforce depends on rates of unemployment and the cost of the employer to replace the worker (53). This issue did not arise in any of the studies reviewed, as the patient populations studied did not include either temporarily or permanently totally disabled individuals.

Use of comparators

In some (increasingly rare) situations the appropriate comparator is the do-nothing option. More often, the appropriate comparison for a treatment is either the best currently available alternative, or the commonly used alternative. Generally the criterion is to use the comparator technology that the new technology is most likely to replace. Use of an appropriate comparator ensures that the results of the analysis are useful to decision-makers. To pose added problems, the appropriate comparator often evolves over time, as appropriate or accepted treatment changes. For example, the use of inhaled anti-inflammatory medications has become more important since the early 1990s, and the frequent use of bronchodilators has become an indication of poor asthma control rather than daily prophylactic therapy.

The Rutten-van Mölken study of budesonide therapy in children used $ß_2$ agonists alone as a comparator (25). However, this study was published in 1993, the use of $ß_2$ agonist as a comparator could be criticised because bronchodilator therapy alone is no longer considered appropriate or normal therapy in asthmatic children with the degree of airway reactivity in the group studied. To be useful for decision-makers new asthma drug treatments should be compared to the recommended treatments in the guidelines for treatment of asthmatics. For moderate to severe asthma, inhaled anti-inflammatory use will certainly be the usual or preferred therapy, and thus the appropriate comparator will be the inhaled anti-inflammatory regimen. A recent evaluation of fluticasone in children with asthma used cromoglycate as a comparator (27) but budesonide or beclomethasone would have been justified.

Dealing with uncertainty

The question of uncertainty can be dealt with using sensitivity analyses, for example in a study comparing emergency department delivery of bronchodilators, the results showed a very small (less than US$1) cost advantage of metered-dose inhaler over nebulizer (19). The results were sensitive to the time required to administer the nebulizer, and whether the metered-dose inhalation could be self-administered. In the circumstances of the particular study, metered-dose inhaler was more cost-effective unless nebulizer administration took less than 4 minutes of supervision and only if the patients were able themselves to administer the inhaler.

Comparing fenoterol to salbutamol (29) two types of sensitivity analyses were performed. The results were expressed in terms of an alternative scenario, which did not reverse the order of the two treatments, but it did reduce the incremental cost per EFD of formoterol over salbutamol. The sensitivity analysis increasing the cost of adverse events increased the difference between the two, as formoterol treatment had slightly higher average adverse event days than salbutamol treatment.

Population used and time frames

An important aspect of the usefulness of the information generated from any study is how easily it can be generalised. Often analyses will be conducted in limited or specially defined populations under particular conditions which limit the usefulness of the conclusions to be drawn from the study (50). This could be particularly important in asthma treatments, as the effects are measured in pre-selected samples, usually asthmatics which are relatively stable, compliant to therapy, well able to administer medications and treated by physicians with expertise in asthma care. Those qualities are not so uniformly distributed in populations outside of clinical trial settings.

The effect of the length of the studies can be seen in the differences seen in the items measured over short-term clinical trials, in which no asthma-related hospitalisations were seen (27) when compared with the trials which

are carried out over a number of years(23, 25) or the public databank records reviews (17).

The particular strength of some pharmacoeconomic analyses is often the interpretation of the test results, by the use of modelling to estimate the impact of a treatment on resource utilisation and health outcomes in populations approximating the real population to be treated and under conditions approaching normal use, rather than randomised clinical trial conditions.

Importance of pharmacoeconomic studies

It is relatively easy to apply the results of cost-minimisation studies providing the test conditions are similar to the practitioners' patients and practice. The series of in-patient bronchodilator studies are cases in point. The least costly alternative, metered-dose inhaler, is the alternative of choice under most assumptions. The same can be said for treatments which are shown by cost-effectiveness or cost-utility studies to be more effective and not more costly than others are, or which are less costly and no less effective. Thus, formoterol has been seen as more cost-effective compared to cromoglycate in children (27), and bronchodilator alone more cost-effective than bronchodilator with ipratropium (23).

The difficulty is when the treatment is both more effective and more costly than an alternative and this is very often the case in the pharmacoeconomic

literature. The question then becomes whether the increase in effect is worth the increased cost. That is the opportunity cost decision and it depends on what alternatives exist for spending that money. In many jurisdictions the increased cost when inhaled corticosteroid is added to bronchodilator treatment in moderate asthmatics will be deemed appropriate in view of the increased effect (23, 25) but this may not hold true for very mild asthmatics where the incremental cost per effect would be higher than seen in those more severely affected, or in some developing countries where healthcare dollars are extremely scarce.

Even though pharmacoeconomic studies are often geared to health program administrators, they may be of relevance to both the individual practitioner in his or her practice. First, if the practitioner examines the results from the point of view of his or her patient, the cost of treatment has an impact, both in terms of purchase of healthcare (or part-purchase if costs are borne by public or private insurers), and the cost of time lost to illness. Secondly, the practitioner plays a social role because of the impact his or her practice decisions have on costs of healthcare. Resources are limited, and choosing the most efficient use of resources can lead to the freeing up of resources for other purposes, whether or not spent on health. The latter notion is that of opportunity cost, each dollar spent on something means that it cannot be spent on other things. This notion applies to the treatment decisions of physicians whose responsibility is not just to the patient before them, but to their other patients, both current and future (51).

Areas for further development

Progress has been made in some of the important issues in pharmacoeconomics in asthma treatment, such as the proposition of episode-free days as a measure of effect that can be used to compare treatments, and the demonstration of the importance of the impact of hospital costs on the variation in cost measurement. More work in the area of disease measures that are useful for comparing asthma treatments to other healthcare interventions is needed. No cost-effectiveness studies have been reported using quality of life measures, particularly those which are generic and not disease-specific. There are measurement and reliability concerns with these generic measures, but the authors do not agree with the suggestion (36) that they not be used. It may be that differences and changes in overall health status in non-severe asthma are difficult to detect with generic instruments which are often designed for short-term but debilitating disease conditions. If so, perhaps research should concentrate on the development of instruments more appropriate for chronic illness, such as asthma, arthritis, and migraine which can detect smaller changes over greater periods.

The wide variation seen in the published literature also poses a problem for decision-makers. In addition to the methodological problems of certain studies, there is inconsistency in the effect measures and in the costs accounted for which do not allow for comparison between studies.

Although a few of the reports are of longer-term studies, the usefulness of short-term clinical trial information on the economic impact of a chronic disease such as asthma is questionable. There are also problems with the ability to apply such trial-based information to normal treatment conditions and to the wide variation in the population encountered in clinical practice, a common criticism also levelled at the results of randomised clinical trials.

Research Agenda

- Develop an outcome measure for asthma treatments which can be used to compare their cost-effectiveness with that of other healthcare interventions
- Incorporate instruments which measure quality of life in studies estimating cost-effectiveness of treatments
- Pursue studies over longer time frames
- Incorporate real-life conditions and patient characteristics in studies evaluating cost-effectiveness of asthma treatments

Table 1 Summary of studies referenced

Ref no	Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
Medications							
[15]	Adelroth & Thompson	36 oral steroid dependant asthmatic adults	Cost evaluation; 5 year cohort, before and after, retrospective and prospective	Budesonide (BUD)	Use of oral steroids	Inpatient days (INP), outpatient visits (OUP), annual medical care (AMC)	75% decrease INP 14% increase OUP 55% reduction AMC
[16]	Ross et al	53 (mostly) children with documented history of asthma	Cost evaluation; 3 years plus prospective cohort, before and after	Cromoglycate (CRO); other anti-asthma medications	None	Physician visits, medications, hospital admissions, emergency room visits	Similar medication costs and physician visits; lower emergency visits, hospitalisations and overall resource use in users of cromoglycate ($1,337 difference per patient per year)
[20]	Perera	86 children with asthma never having used inhaled steroids	Cost evaluation, cost-consequence; 2-year before and after	Beclomethasone or budesonide (CST)	Breakthough wheezing, acute severe attacks, hospital admissions, loss of schooling, satisfaction of parents	Retrospective resources use of 1 year at start and end of study (physician visits, drugs, hospital admissions, travelling, loss of revenue)	Significant change in all effect measures after introduction of inhaled steroids post- CST cost saving of £20 per month pre-CST £3.50 per unit of satisfaction, post-CST £0.07 per unit
[17]	Tierce et al	1463 patients with more than 1 asthma diagnosis using salbutamol (SAL) or orciprenaline (ORC) bronchodilators only	Cost evaluation; retrospective review of Medicaid data	Salbutamol (SAL) orciprenaline (metaproterenol) (ORC)	None	Asthma medications; and asthma-related hospital admissions, physician visits, and emergency room visits	No difference in medication costs; lower physician vists, emergency room visits, hospitalisation costs and overall resource use in salbutamol users ($370 difference per patient per year)

Table 1 Continued

Ref no	Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
[29]	Sculpher & Buxton	145 asthmatics needing daily bronchodilator	Cost-effectiveness; Randomised Double-Blinded multicentre	Formoterol aerosol (FMT); salbutamol (SAL) aerosol	Episode-free days (EFD), adverse-event days, mean salbutamol use	Study drugs rescue drug (SAL)	No difference ($p<0.05$) in effect; FMT $2.20 per EFD; SAL $1.40 per EFD ; FMT over SAL $7.29 per additional EFD
[25]	Rutten-van Molken et al	116 children with asthma	Cost-effectiveness; 3 year randomised, double-blinded parallel multicentre	SAL with one of: budesonide (B2+BUD) or placebo (B2	FEV1 % predicted, SFD, days absent from school,	Study drugs, rescue drugs, (other asthma related drugs), physician contacts, hospitalisations, indirect costs of school absences (not included in c/e ratio)	Conservative analysis B2+BUD more costly and more effective than B2: f.175 per 10% increase in FEV1 per year; f.92 per day of school absence; f.10 per SFD
[23]	Rutten-van Molken et al	274 adults with asthma or COPD	Cost-effectiveness; 2.5 year randomised, double-blinded parallel multicentre	Terbutaline (TER) with one of: beclomethasone (TER-BEC), ipratropium (TER-IPR) or placebo (TER)	FEV1 % predicted, symptom-free days (SFD),	Related to asthma or COPD: study drugs, rescue drugs (oral steroids, SAL, antibiotics, other), physician contacts, hospitalizations	TER-BEC more costly and more effective than TER: $200 per 10% increase in FEV1; $5.35 per SFD (95% CI: $1-$127); TER-IPR more costly and no more effective than TER
[27]	Booth et al	125 asthmatic children not having used prophylatic inhalation therapy	Cost-effectiveness; 8-week randomised, open, parallel, multicentre	Fluticasone (FLUT) cromoglycate (CRO)	Proportion of successfully treated patients (adverse reaction and either day or night symptom free, or PEFR ≥ 90% predicted morning or evening)	Study drugs, rescue drugs, asthma-related hospitalisation	FLUT both more effective and less costly than CRO; average cost to treat per success was £25 FOR FLUT and £63 for CRO, £27 per success less for FLUT
[28]	*Thomas et al	Asthmatics using MDI bronchodilator	Cost-effectiveness, cost-minimisation; randomised, double-blinded crossover	Oral SAL placebo	PEFR, quality of life	Inhaled bronchodilator and oral SAL	Oral SAL no more effective; cost to patient was 20 rubles per month for oral SAL

Ref no	Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
[26]	*Campbell et al	556 teenage and adult asthmatics	Cost-effectiveness, cost-minimisation; 12-week, randomised, double-blinded, crossover	Two dosage levels of inhaled budesonide: 400 and 800 µg per day	Lung function, asthma symptoms (PEFR) (cough, disturbed sleep)	Study medications only	Effect no different; cost of 800µg per day higher than 400 by £1450
[24]	*Connett et al	40 young children with persistant asthma symptoms	Cost-effectiveness; 6 month randomised	Inhaled budesonide (BUD) placebo	Symptom-free days (SFD)	Direct medical costs and indirect costs	BUD more effective than placebo and less costly by £6.33 per SFD
Delivery systems							
[18]	Bowton et al	Overall treatment of respiratory patients in tertiary-care hospital	Cost evaluation; 7 month prospective before and after study of one hospital centre	ß-agonist therapy policy of substitution of MDI for NEB except cases where judged inappropriate or no-sub order	None	Patient drug charges; hospital drug costs and salary costs of respiratory therapists	(After policy over 60% of patients were on MDI) annual savings to patients (based on charges) of #396,000; annual potential cost saving of $139,000 (at least $32,000 based on 95% CI)
[21]	Jasper et al	34 adult patients hospitalised with obstructive airways disease after emergency treatment	Cost-minimization; randomised open single centre	Orciprenaline (metaproterenol) by updraft nebulization (NEB) or metered-dose inhaler (MDI)	FEV_1 & FVC (initial, post-bronchodilator and final), days of hospitalisation	Treatments with orciprenaline (drug and administration costs)	Annual cost of treatment at the study hospital with MDI would be $253,000 less per year than with NEB
[22]	Summer et al	32 adult patients hospitalised with obstructive airways disease after emergency treatment	Cost-minimization; randomised open single centre	Orciprenaline by updraft nebulization (NEB) or terbutaline by metered-dose inhaler (MDI)	FEV_1, FVC, FEV_1/FVC, PEF (pre-treatment, and 45 minutes and 5 hours after treatment) length of hospital stay and treatment	Patient drug charge; hospital salary cost of respiratory therapist time	Response to MDI at least equivalent to NEB in 23 or 24 effect comparisons made charges $3145 more in UDN group salary cost $470 more in UDN group

Table 1 Continued

Ref no	Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
[19]	Turner et al	95 adult patients on bronchodilator therapy in one hospital	Cost evaluation; descriptive prospective study of cohort of all eligible patients admitted over 6 week period	MDI delivered salbutamol or ipratropium; NEB delivery of salbutamol; combination of MDI & NEB	None	Medication costs to hospital (incl labour), labour costs of nurses, equipment costs of NEB and spacers for MDI	MDI costs $0.89 per treatment less than equivalent NEB treatment MDI less costly if self-administration possible and if > 4 minutes needed for NEB administration

*Although included in this table, these studies have not been reviewed for the article.

REFERENCES (The numbered references are for the article only, the balance are found at the end of the thesis.)

1. Milne RJ. Evaluation of the Pharmacoeconomic Literature. *PharmacoEconomics* 1994; **6**: 337-345.

2. Revicki DA. Relationship of pharmacoeconomics and health-related quality of life. In: Spilker B, (ed) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 1077-1083.

3. Drummond M. The emerging government requirement for economic evaluation of pharmaceuticals. *PharmacoEconomics* 1994; **6**(Supplement 1): 42-50.

4. Rutten-Van Molken MP, Van Doorslaer EK., Rutten FF. Economic appraisal of asthma and COPD care: a literature review 1980-1991. *Soc Sci Med* 1992; **35**: 161-175.

5. Bryan S, Buxton MJ. Economic evaluation of treatments for respiratory disease. *PharmacoEconomics* 1992; **2**: 207-218.

6. Mellis CM, Peat JK, Woolcock AJ. The cost of asthma Can it be reduced? *PharmacoEconomics* 1993; **3**: 205-219.

7. Sullivan S, Elixhauser A, Buist AS, Luce BR, Eisenberg J, Weiss KB. National Asthma Education and Prevention Program working group report on the cost effectiveness of asthma care. *Am J Resp Crit Care Med* 1996; **154**: S84-95.

8. Sullivan SD. Cost-effectiveness of drug interventions. *Eur Resp Rev* 1996; **6**: 116-118.

9. Buxton MJ. The economics of asthma -- an introduction. *Eur Resp Rev* 1996; **6**: 105-107.

10. Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care progammes.* Oxford: Oxford University Press, 1987:

11. Torrance GW, Siegel JE, Luce BR. Framing and Designing the Cost-Effectiveness Analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC (eds) *Cost-Effectiveness in Health and Medicine.* Oxford: Oxford University Press, 1996: 54-81.

12. Freund DA, Dittus RS. Principles of Pharmacoeconomic Analysis of Drug Therapy. *PharmacoEconomics* 1992; **1**: 20-31.

13. Canadian Coordinating Office for Health Technology Assessment. *Guidelines for economic evaluation of pharmaceuticals.* Ottawa. November 1994.

14. Torgerson DJ, Spencer A. Marginal costs and benefits [see comments]. *BMJ* 1996; **312**: 35-6.

15. Adelroth E, Thompson S. Advantages of high-dose inhaled budesonide. *Lancet* 1988; **1**: 476.

16. Ross RN, Morris M, Sakowitz SR, Berman BA. Cost-effectiveness of including cromolyn sodium in the treatment program for asthma: a retrospective, records-based study. *Clin Ther* 1988; **10**: 188-203.

17. Tierce JC, Meller W, Berlow B, Gerth WC. Assessing the cost of albuterol inhalers in the Michigan and California Medicaid programs: a total cost-of-care approach. *Clin Ther* 1989; **11**: 53-61.

18. Bowton DL, Goldsmith WM, Haponik EF. Substitution of Metered-dose Inhalers for hand-held Nebulizers Success and cost savings in a Large, Acute-care Hospital. *Chest* 1992; **101**: 305-308.

19. Turner MO, Gafni A, Swan D, FitzGerald JM. A review and economic evaluation of bronchodilator delivery methods in hospitalised patients. *Arch Int Med* 1996; **156**: 2113-2118.

20. Perera BJC. Efficacy and cost effectiveness of inhlaed steroids in asthma in a developing country. *Arch Dis Child* 1995; **72** :312-316.

21. Jasper AC, Mohsenifar Z, Kana S, Goldberg HS, Koerner SK. Cost-benefit comparison of Aeorsol bronchodilator delivery methods in hospitalised patients. *Chest* 1987; **91**: 615-618.

22. Summer W, Elson R, Tharpe L, Nelson S, Haponik EF. Aeorosol Bronchodilator Delivery Methods. *Arch Int Med* 1989; **149**: 618-623.

23. Rutten van-Mölken MP, Van Doorslaer EK, Jansen MC, Kerstjens HA, Rutten FF. Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1995; **151**: 975-982.

24. Connett GJ, Lenney W, McConchie SM. The cost-effectiveness of budesonide in severe asthmatics aged one to three years. *Br J Med Econ* 1993; **6**:127-134.

25. Rutten van-Mölken MP, van Doorslaer EKA., Jansen MCC, Van Essen-Zandvliet EE, Rutten FFH. Cost-effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator

monotherapy in children with asthma. *PharmacoEconomics* 1993; **4**: 257-270.

26. Campbell LM, Simpson RJ, Turbitt ML, Richardson PDI. A comparison of the cost-effetiveness of budesonide 400 µg/day and 800 µg/day in the management of mild to moderate asthma in general practice. *Br J Med Econ* 1993; **6**: 67-74.

27. Booth PC, Wells NEJ, Morrison AK. A comparison of the cost effectiveness of alternative prophylactic therpaies in childhood asthma. *PharmacoEconomics* 1996; **10**: 262-268.

28. Thomas K, Peter JV, Cherian AM, Guyatt G. Cost-effectiveness of inhaled beta-agonists v. oral salbutamol in asthma: a randomised double-blind cross-over study. *Nat Med J India* 1996; **9**: 159-162.

29. Sculpher MJ, Buxton M. The episode-free day as a composite measure of effectiveness: an illustrative economic evaluation of formoterol versus salbutamol in asthma therapy. *PharmacoEconomics* 1993; **4**: 345-352.

30. Gold MR, Patrick DL, Torrance GW, Fryback DG, Hadorn DC, Kamlet MS, Daniels N, Weinstein MC. Identifying and Valuing Outcomes. In: Gold MR, Seigel JE, Russell LB, Weinstein MC (eds) *Cost-effectiveness in Health and Medicine*. New York: Oxford University Press, 1996: 82-134.

31. Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ* 1986; **5**: 1-30.

32. Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res* 1972; **7**: 118-133.

33. Torrance GW, Furlong W, Feeny D, Boyle M. Multi-Attribute Preference Functions Health Utilities Index. *PharmacoEconomics* 1995; **7**: 503-520.

34. Group EuroQol. EuroQol: a new facility for the measurement of health-related quality of life. *Health Pol* 1990; **16**: 199-208.

35. Kind P. The EuroQoL instrument: an index of health-related auality of life. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 191-201.

36. Richards JM, Hemstreet MP. Measures of life quality, role performance, and functional status in asthma research. *Am J Respir Crit Care Med* 1994; **149**: S31-39.

37. Rutten van-Mölken MP, Custers F, van Doorslaer EK, Jansen CC, Heurman L, Maesen FP, Smeets JJ, Bommer AM, Raaijmakers JA. Comparison of performance of four instruments in evaluating the effects of salmeterol on asthma quality of life. *Eur Resp J* 1995; **8**: 888-898.

38. Johannesson M, Weinstein MC. Designing and conducting cost-benefit analyses. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 1085-1092.

39. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ* 1994; **3**: 95-104.

40. Marks G, Dunn SM, Woolcock AJ. A scale for the measurement of quality of life in adults with asthma. *J Clin Epid* 1992; **45**: 461-472.

41. Juniper EF, Guyatt GH. Asthma and Allergy. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials.* 2nd edn. Philadelphia: Lippincott-Raven, 1996: 977-982.

42. Juniper EF, Guyatt GH, Griffith LE. Measuring quality of life in asthma. *Am Rev Resp Dis* 1993; **147**: 832-838.

43. Russell LB, Siegel JE, Daniels N, Gold MR, Luce BR, Mandelblatt JS. Cost-Effectiveness Analysis as a Guide to Resource Allocation in Health: Roles and Limitations. In: Gold MR, Seigel JE, Russell LB, Weinstein MC (eds) *Cost-effectiveness in Health and Medicine.* New York: Oxford University Press, 1996: 3-24.

44. Lofdahl C-G. Cost development of obstructive airway disease in Sweden. *Eur Resp Rev.* 1996; **6**: 113-115.

45. Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada, 1990. *Can Med Assoc J* 1996; **154**: 821-831.

46. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med* 1992; **326**: 862-866.

47. Mellis CM, Peat JK, Bauman AE, Woolcock AJ. The cost of asthma in New South Wales. *Med J Aust* 1991;**155**: 522-528.

48. Rutten-van Mölken MP, van Doorslaer EK, van Vliet RCJA. Statistical Analysis of cost outcomes in a randomised controlled clinical trial. In: *Costs and effects of pharmacotherapy in asthma and COPD.* Maastricht: Maastricht University, 1994: 170-189.

49. Posnett J, Jan S. Indirect cost in economic evaluation: the opportunity cost of unpaid inputs. *Health Econ* 1996; **5**: 13-23.

50. Rittenhouse BE, O'Brien BJ. Threats to the validity of pharmacoeconomic analyses based on clinical trial data. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials.* 2nd edn. Philadelphia: Lippincott-Raven, 1996: 1215-1223.

51. Davey P, Malek M. The impact of pharmacoeconomics on the practitioner and the patient. *PharmacoEconomics* 1994; **6**: 298-309.

52. Koopmanschap MA, Rutten FFH. A practical guide for calculating indirect costs of disease. *PharmacoEconomics* 199; **10**: 460-466.

3.4 An update of the literature review

The revised table (table 3.2) summarises the articles contained in this update, in addition to those dealing with medications which were found in the original review article. The section on delivery systems has not been included, and no update on this section has been conducted.

3.4.1 Cost-evaluation, cost-consequence studies

Stempel et al., (1996) looked at the impact of high use of bronchodilators (defined as 8 or more puffs per day) on use and cost of anti-asthma health services, using a retrospective 12 month review of the medical claims information of 4 health maintenance organisations. When compared to average asthmatics, the cost of anti-asthma health services of high bronchodilator users was 3.0 times higher ($1,347 vs. $447). The main criticism which could be levelled at this study was the uncertainty that all the subjects were, in fact, asthmatic, as the inclusion criteria relied on a single medical claim for asthma, or two or more prescriptions of a anti-asthma medication. The study looked at three categories of these users of large quantities of bronchodilators, based on the quantity of iCSTs. Interestingly, among the high users, the subgroup with no record of iCST consumption had the lowest level of cost of office visits and hospitalisations, even though their medication costs were still higher than the average asthma patient, which may indicate the rate of bronchodilator use in this group was not a good indication of severity of asthma. The results, however, which

compared the group with what was termed 'adequate' iCST dose (4 or more puffs per day) with the group with inadequate dose (receipt of iCST but less than 4 puffs per day), were consistent with the theory that adequate iCST use would result in lower cost of other asthma related health services: the 'inadequate' group had higher use of oral steroids, emergency services and hospital services.

Using a retrospective analysis of Medicaid claims data in a case-control study, Balkrishnan et al. (1998) studied the use and cost of health services in a group of 85 asthmatic children who started iCST therapy and continued for at least 1 year. Their use of health services during the period one year before and one year after they started iCST therapy was assessed and compared to controls (n=72) matched for use of anti-asthma therapy. Both cases and controls had received a physician service coded as asthma. A significant ($p<0.1$) decrease in hospital and physician services, and a non-significant decrease in outpatient services were seen in the iCST group, but not the control group who registered an increase in those services (significant in the case of outpatient services only). The regression analysis assessing the effect of group on natural log of monthly Medicaid health costs, found cost savings of 25% in the cases compared with controls, controlling for age, gender, group, time and comorbidity variables. There was no control for disease severity in this study, and the validity of the diagnosis of asthma is uncertain.

The same authors repeated the same study design in the Medicaid users of all ages, and found similar results (Balkrishnan et al., 1988). Cases (n=233) were chosen if they started iCST therapy within a given time window, and used it continuously for one year thereafter. Controls (n=180) were matched for use of anti-asthma therapy. Both cases and controls had received a physician service coded as asthma. A significant ($p<0.1$) decrease in hospital, physician services, and outpatient services were seen in the iCST group, but not the control group who registered an increase in those services (significant in the case of hospital and outpatient services, but not in the case of physician services). The regression analysis assessing the effect of group on natural log of monthly Medicaid health costs, found cost savings of 24% in the cases compared with controls, controlling for age, gender, group, diagnoses, comorbidity and year variables. There was a control for disease severity in this study, the subjects were deemed moderate if the diagnostic codes were simple asthma, but if any diagnosis of COPD (ICD-9 codes 491.20 or 491.21) were found, they were assumed to be severe. The use of diagnostic codes as a severity indication was not validated, and there is a likelihood that the inclusion of COPD codes may have complicated the analysis with the presence of non-asthmatics.

A pre-post case-control study of asthmatic patients in a general practice clinic looked at the use and cost of health services for one year before and

after the patient started on fluticasone (Price & Appleby, 1998). Both cases and controls could have been taking other iCSTs prior to starting on fluticasone. The controls were chosen from individuals started later on fluticasone. Cases (n=21) showed and increase in PEF, and a decrease in bronchodilator use, oral steroid use, and physician visits. Controls (n=24) showed increases or no change. Costs stayed about the same in the cases (an average increase of £ 2), representing an increase in average drug costs (£ 91) and a decrease in other average costs (£ 90). Controls had lower costs overall, but an increase of £ 61 on average was noted, of which £ 46 were drugs and £ 15 consultations. Again, the two groups may not have been equivalent, although the authors indicated similar demographics and the same median dosage of iCST prior to enrolment in the study.

3.4.2 Cost-minimisation studies

A study comparing two regimens of budesonide treatment with fluticasone treatment (Venables et al., 1996) found no significant difference in the effect of the treatments, which then turned the study into a cost minimisation. The study compared once-daily (74 subjects) and twice-daily (74 subjects) budesonide (400µg) with twice daily (73 subjects) fluticasone (400µg) and measured the percentage of symptom-free-days (SFD) and percentage of days with 5% or greater improvement in lung function (PEF). The only costs measured were those of anti-asthma medications. Costs for relief medication were lowest, but not significantly so, in the fluticasone group (£

5 vs. £ 8 in the other two groups), adverse event medication was lowest (again not significantly) in the once-daily budesonide group (£ 0.8 vs. £ 1.5 in the twice daily budesonide and £ 1.2 in the fluticasone groups). However, when the iCST costs were added, the overall costs were higher in the fluticasone group (£ 56 vs. £ 30 in the once-daily budesonide £ 31 and in the twice-daily budesonide group). The weaknesses of this study were mainly the short duration for a long-term therapy, and the fact that other asthma-related health services was not considered.

In a group of 30 users of inhaled bronchodilators, Thomas and colleagues (1996)[3] compared oral salbutamol with placebo in an RCT (crossover) of 7 weeks duration. There was no difference between the two treatments in the main measure of lung function (PEFR of 235 vs. 232 ml/minute), and none in the quality of life score (162 vs. 160). The study was therefore analysed as a cost-minimisation. Use of inhalers in the treatment period was lower than the placebo period group by weight (p=0.08), and by number of puffs (18 vs. 22.5), but the cost was 20 Rubees higher per month due to the addition of the oral salbutamol.

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[3] This study was summarised in the original table of the article, but the authors had only an abstract, so it had not been included in the article itself.

3.4.3 Cost-effectiveness studies

Connett et al. 1993[4] compared budesonide 400 to 800 µg per day to placebo in 40 asthmatic children aged 1 to 3 years in a 6 month-long blinded RCT. All children could use terbutaline on an as needed basis. Results were measured primarily in symptom-free days (SFD), and the study found budesonide to be both more effective and less costly than placebo, with a cost saving of £ 6 per additional SFD. On an annual basis, both direct and indirect costs were higher with placebo, as were most components of these categories. The exception was the total annual drug costs, which were higher in the budesonide group (£ 149 vs. £ 48). This difference was due to the cost of the iCST, because the non-budesonide drug costs were similar in both groups (£ 19 for placebo vs. £ 18 for budesonide). This study would probably not be repeated currently, because the use of placebo as a comparator would not be seen as appropriate.

Steinmetz and colleagues (1998) studied the effect of fluticasone and budesonide in 457 asthmatic subjects for 6 weeks in an open label RCT. Cost data was gathered retrospectively, and included costs of study medication, additional anti-asthma medications, medications to treat adverse-events, office-based physician visits, and hospitalisations.

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[4] This study was also only available in abstract form for the original article.

Fluticasone cost DM10.58 per SFD, compared to DM15.26 for budesonide. Sensitivity analyses varying the total treatment cost (± 20%), PEFR (± 10%), and the reduction in the price (-30%) and number of puffs (from 6 to 5) of budesonide, did not change the order of results. The study was of short duration for a chronic treatment.

The Hall and colleagues study (1992) is an abstract only, and the details of the methodology and results are missing. However, using an RCT design and measuring the costs of medications (study drug, relief medication) and physician visits, the researchers compared salmeterol 50μg twice daily (n=80) to salbutamol 400μg twice daily (n=67). The main effect measure was the number of subjects symptom-free in the final week of the study. Symptom free was estimated in three ways: no symptoms, 90% or greater PEF in the morning, and 90% or greater in the evening. There were more subjects symptom free in the salmeterol group according to the first method of assessment (62% vs. 40%), the second method (37% vs. 12%) and the third method (36% vs. 20%). Cost per symptom free subject were higher in the salbutamol group according to the first method (£ 523 vs. £ 405) and the third method (£ 900 vs. £ 810), but not the second (£ 876 vs. £ 1350).

In Booth et al. (1995), 269 adult asthmatics, who had either never received inhaled corticosteroids or had received up to 600μg per day of budesonide or beclomethasone, were randomised to receive one of the two study drugs

for 8 weeks. Effect was measured by the average proportion of successfully treated weeks, measured as a week during which the patient's PEF predicted improved at least 5%. Costs consisted of the costs for use of study drugs, rescue medications and asthma-related adverse events. Fluticasone (200µg twice daily) was seen to be more effective than budesonide (400µg twice daily) and more costly. The cost per treatment week was slightly less for fluticasone (£11.18 vs. 11.98). The results remained robust to a sensitivity analysis which varied the definition of successfully treated week in terms of percentage of PEF improvement. This study does not appear to have been analysed on an intention to-treat-basis. The range of costs measured was very limited, and did not take into account the cost to treat non-medication anti-asthma costs.

3.5 Overall conclusions from the literature with respect to the economic impact of iCSTs

The majority of published studies reviewed associate lower overall healthcare costs with the use of iCSTs: Adelroth & Thompson, 1984; Connett et al., 1993; Booth et al., 1996; Perera, 1995; Balkrishnan et al., 1998a; Balkrishnan et al., 1998b. Two other studies showed an increase in overall costs associated with the use of iCSTs, partially offset by a decrease in health care costs other than the iCSTs: Rutten-van Mölken et al., 1993; Rutten-van Mölken et al., 1995. Of those studies comparing use of iCSTs to other anti-asthma medications (or placebo) four of these studies were RCTs (Rutten-van Mölken et al., 1993 and 1995; Booth et al., 1996;

Connett et al., 1993). The balance (Adelroth & Thompson, 1984; Balkrishnan et al., 1998a; Balkrishnan et al., 1998b), were retrospective analyses using electronic data created for billing purposes.

Of the RCTs, the Rutten-van Mölken et al. studies included more types of costs than the others, including not only the usual range of anti-asthmatic medications, but homeopathic and cough and cold preparations. The Connett study appears to have included all recorded anti-asthma medications, including antibiotics and cough suppressants, and the Booth study included only study medications (iCST, cromoglycate and rescue salbutamol). The other health services included in the Connett and Rutten-van Mölken studies appeared to have been the same, and the Booth study included only hospitalisations. The use of health services in these studies is normally from patient reporting during the trial follow-up visits, or from patient records.

The studies which determined their costs from retrospective analysis of data base information are restricted by the information which is available. The use of medications in the retrospective analyses are based upon prescriptions dispensed, with the exception of the Price & Appleby study which used prescriptions given to the subjects. Estimation of true medication use is particularly difficult, all of the three methods encountered are to a certain extent unrepresentative of true consumption.

Although the studies of the economic impact of interventions to treat asthma are concerned with measuring the reduction of emergency room visits, clinic visits, and hospital care days, many studies demonstrate that the average hospitalisation cost is affected by a small number of severe cases, so that testing differences in hospitalisation costs is difficult unless the sample size is large enough to overcome this statistical power problem (Rutten-van Mölken et al., 1992). Generally, this outcome is restricted to very large RCTs, those involving subjects with a high rate of hospitalisation (thus relatively severe, uncontrolled asthmatics), or retrospective analysis of electronic data bases, involving a large number of subjects.

Although the number of subjects available for study in retrospective analyses is relatively large, these may suffer from problems of confounding due to indication. The pre-post studies, even when using a control group or controlling for differences, may not compare utilisation in equivalent groups. For example, in the Balkrishnan studies it is not certain that a differing selection criteria did not apply to the subjects who received iCSTs, and those who did not.

However, the evidence is relatively uncontrovertable that treatment regimens involving iCST therapy compared to those which do not, are efficacious (data from the RCTs) and effective (data from the retrospective analyses). They may or may not be less costly. The cost of the therapy will

depend upon the subjects used to measure those costs, and the costs measured, as well as the type of study.

The literature has confirmed the appropriateness of the case study of iCST users in asthma for the purposes of the questions we posed. The costs of iCSTs form an important element in the overall burden of the disease. ICST use had been associated with a decrease in the use of rescue medications and other health care services and costs. We should be able to explore our question of the RCT construct by examination of the use and cost of anti-asthma health services in the different settings and different samples of subjects.

Table 3.2 Revised summary of studies referenced

Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
*Adelroth & Thompson 1988	36 oral steroid dependant asthmatic adults	Cost evaluation; 5 year cohort, before and after, retrospective and prospective	Budesonide (BUD)	Use of oral steroids	Inpatient days (INP), outpatient visits (OUP), annual medical care (AMC)	75% decrease INP 14% increase OUP 55% reduction AMC
Ross et al 1988	53 (mostly) children with documented history of asthma	Cost evaluation; 3 years plus prospective cohort, before and after	Cromoglycate (CRO); other anti-asthma medications	None	Physician visits, medications, hospital admissions, emergency room visits	Similar medication costs and physician visits; lower emergency visits, hospitalisations and overall resource use in users of cromoglycate ($1,337 difference per patient per year)
Tierce et al 1989	1463 patients with more than 1 asthma diagnosis using salbutamol (SAL) or orciprenaline (ORC) bronchodilators only	Cost evaluation; retrospective review of Medicaid data	Salbutamol (SAL) orciprenaline (metaproterenol) (ORC)	None	Asthma medications; and asthma-related hospital admissions, physician visits, and emergency room visits	No difference in medication costs; lower physician vists, emergency room visits, hospitalisation costs and overall resource use in salbutamol users ($370 difference per patient per year)
*Hall et al 1992	147 patients with moderate asthma	Cost-effectiveness; RCT blinded parallel	Salmeterol 50 twice daily, SAL 400 twice daily	Symptom free subjects in final study week, subjects with 90% PEFR (AM and PM) in final study week	Study medications, rescue medications, physician visits,	Salmeterol saw 62% of subjects symptom free, to 40 of SAL subjects Cost per effectively treated patients (symptom-free) was £523 with Salmeterol and £405 with SAL. The results for effectively treated patients using PM PEF were in the same direction, but using AM PEF they were opposite.

*Abstract only

Table 3.2 Continued

Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
Campbell et al 1993	556 teenage and adult asthmatics	Cost-effectiveness, cost-minimisation; 12-week, randomised, double-blinded, crossover	Two dosage levels of inhaled budesonide: 400 and 800 µg per day	Lung function, asthma symptoms (PEFR) (cough, disturbed sleep)	Study medications only	Effect no different; cost of 800µg per day higher than 400 by £1450
Connett et al 1993	40 young children with persistant asthma symptoms	Cost-effectiveness; 6 month randomised	Inhaled budesonide (BUD) placebo	SFD	Direct medical costs and indirect costs	BUD more effective than placebo and less costly by £6.33 per SFD
Rutten-van Molken et al 1993	116 children with asthma	Cost-effectiveness; 3 year randomised, double-blinded parallel multicentre	SAL with one of: budesonide (B2+BUD) or placebo (B2	FEV1 % predicted, SFD, days absent from school,	Study drugs, rescue drugs, (other asthma related drugs), physician contacts, hospitalisations, indirect costs of school absences (not included in c/e ratio)	Conservative analysis B2+BUD more costly and more effective than B2: f.175 per 10% increase in FEV1 per year; f.92 per day of school absence; f.10 per SFD
Sculpher & Buxton 1993	145 asthmatics needing daily bronchodilator	Cost-effectiveness; Randomised Double-Blinded multicentre	Formoterol aerosol (FMT); salbutamol (SAL) aerosol	Episode-free days (EFD), adverse-event days, mean salbutamol use	Study drugs rescue drug (SAL)	No difference ($p<0.05$) in effect; FMT $2.20 per EFD; SAL $1.40 per EFD ; FMT over SAL $7.29 per additional EFD
Booth et al 1995	269 adult asthmatics	Cost-effectiveness; 8-week randomised, open, parallel, multicentre	Fluticasone 200µg twice daily (FLUT) Budesonide 400µg twice daily (BUD)	Successfully treated weeks (mean PEFR of the week ≥ 5% predicted)	Study drugs, rescue drugs, medication to treat adverse effects	FLUT more costly than BUD; average cost per successfully treated week 6.7% less for FLUT than BUD.
Perera **1995**	86 children with asthma never having used inhaled steroids	Cost evaluation, cost-consequence; 2-year before and after	Beclomethasone or budesonide (CST)	Breakthough wheezing, acute severe attacks, hospital admissions, loss of schooling, satisfaction of parents	Retrospective resources use of 1 year at start and end of study (physician visits, drugs, hospital admissions, travelling, loss of revenue)	Significant change in all effect measures after introduction of inhaled steroids post- CST cost saving of £20 per month pre-CST £3.50 per unit of satisfaction, post-CST £0.07 per unit

Table 3.2 Continued

Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
Rutten-van Molken et al 1995	274 adults with asthma or COPD	Cost-effectiveness; 2.5 year randomised, double-blinded parallel multicentre	Terbutaline (TER) with one of: beclomethasone (TER-BEC), ipratropium (TER-IPR) or placebo (TER)	FEV1 % predicted, symptom-free days (SFD),	Related to asthma or COPD: study drugs, rescue drugs (oral steroids, SAL, antibiotics, other), physician contacts, hospitalizations	TER-BEC more costly and more effective than TER: $200 per 10% increase in FEV1; $5.35 per SFD (95% CI: $1-$127); TER-IPR more costly and no more effective than TER
Booth et al 1996	125 asthmatic children not having used prophylatic inhalation therapy	Cost-effectiveness; 8-week randomised, open, parallel, multicentre	Fluticasone (FLUT) cromoglycate (CRO)	Proportion of successfully treated patients (adverse reaction and either day or night symptom free, or PEFR ≥ 90% predicted morning or evening)	Study drugs, rescue drugs, asthma-related hospitalisation	FLUT both more effective and less costly than CRO; average cost to treat per success was £25 FOR FLUT and £63 for CRO, £27 per success less for FLUT
Stempel et al 1996	20,512 subjects aged 7 and older, identified as asthmatics	Cost evaluation; 12-month retrospective analysis of medical claims and pharmacy data	High users (8 puffs or more per day) of bronchodilators	Use of asthma-related health services, ED, hospital, physician and medication	Asthma related health services	High users of bronchodilators had costs 3 times higher (($1300 vs. $450) than average asthmatic. Broup with 'inadequate' iCST use had highest costs.
Thomas et al 1996	Asthmatics using MDI bronchodilator	Cost-effectiveness, cost-minimisation; randomised, double-blinded crossover	Oral SAL placebo	PEFR, quality of life	Inhaled bronchodilator and oral SAL	Oral SAL no more effective; cost to patient was 20 rubles per month for oral SAL
Venables et al 1996	221 adult asthmatics	Cost-effectiveness; 8 week randomised	Inhaled BUD 400 µg once per day and 200 µg twice per day, FLUT 200 µg twice per day	% of SFD PEFR	Drug costs for asthma treatment	No difference in effect nor in cost of treatment (net of iCST cost) ICST cost means that FLUT is more costly than BUD

Table 3.2 Continued

Author	Population	Study type	Treatments	Effects measured	Costs measured	Results
Balkrishnan et al 1998a	180 cases and 233 controls Medicaid recipients of all ages identified as asthmatics and users of anti-asthma medications	Cost evaluation; Case control 24-month retrospective analysis of medical claims and pharmacy data	Cases had started iCST therapy during a defined window and continued for 1 year, controls did not use iCST therapy	Change from one year to the next of health care use: hospital, outpatient and physician visits	Total medicaid costs	Cases showed decrease in hospital (significant=s), physician (s), and outpatient visits (s), controls showed an increase in hospital (s), physician (ns) and outpatient (s) visits 24% saving of iCST therapy after adjustment for control variables
Balkrishnan et al 1998b	85 cases and 72 controls Medicaid recipients aged 12 and younger identified as asthmatics and users of anti-asthma medications	Cost evaluation; Case control 24-month retrospective analysis of medical claims and pharmacy data	Cases had started iCST therapy during a defined window and continued for 1 year, controls did not use iCST therapy	Change from one year to the next of health care use: hospital, outpatient and physician visits	Total medicaid costs	Cases showed decrease in hospital (significant=s), physician (s), and outpatient visits (ns), controls showed increase in hospital (ns), physician (ns) and outpatient (s) visits 25% saving of iCST therapy after adjustment for control variables
Price & Appleby 1998	Cases (n-21) vs. controls (n=24) both with diagnosed asthma registed in one GP practice	Cost-consequence; Case control 24-month retrospective analysis of lung function and use of services	Cases had started FLUT during a defined window, controls had started FLUT after the study period	PEF Use of rescue medications (bronchodilators, oral prednisone) GP visits, hospital visits	Total of rescue medications (bronchodilators, oral prednisone) GP visits, hospital visits	Cases showed increase in PEF, decrease in bronchodilator and oral steroid prescriptions, and GP vistits, controls showed either no change or slight increases Hospital visits were too few to be used
Steinmetz et al 1998	457 adults with moderate asthma	Cost-effectiveness; RCT open parallel	FLUT 500 twice daily vs BUD 600 twice daily	Number of subjects with increase in PEFR ≥ 10%, average % of SFD, Physician rated effect	Study medications, rescue medications, adverse event medications, physician visits, hospitalisations	Effect results were all higher in the FLUT group Daily costs lower in FLUT group (DM4.23) than in BUD group (DM5.19); FLUT cost DM11 per SFD, BUD DM15 per SFD

Chapter 4

Methodology and Research Design

The discussion in the previous chapters leads to the final hypotheses concerning the threats to construct validity posed by the RCT as they apply to the ability to generalise the use and cost of health services measured in the RCT involving iCST treatment for asthma.

The literature dealing with the construct validity of the RCT suggests that the subjects in the RCT would have a smaller range of compliance behaviours (are more homogeneous) and would be more adherent to their iCST therapy, behaving differently than they would otherwise, increasing their adherence to iCST therapy (construct validity of the subject). We also surmise that providers of the treatment are more qualified than the providers of similar treatments in real life. The treatment in the trial represents a fixed single example of the possible range of treatments in real life, which emphasises the optimum use of iCST therapy and the minimum use of other treatments (construct validity of the treatment). The medications tested in the clinical trial cost the subjects nothing, and the access to professional care is easier and more comprehensive than in real life (construct validity of the setting).

Considering that the RCT and real life differ in terms of setting, subject and treatment construct, and that the use and cost of health services are a result of

the treatment, these constructs and their interaction, we are led to put forth the following hypotheses:

Specific Hypothesis 1. the use and cost of health services of the asthmatic patient during the RCT will be less variable than that in real life;

Specific Hypothesis 2. the use and cost of health services, other than that of iCST, of the asthmatic patient during the RCT will be lower than that in real life;

Specific Hypothesis 3. the use and cost of iCST therapy of the asthmatic patient during the RCT will be higher than in real life;

therefore, the generalisation of use and cost results from the RCT to real life is extremely difficult.

As argued in Chapter 2, the premise is that with a medication such as iCSTs, and subject to the underlying seriousness of the asthma, a 'theoretical' best possible control of the disease can be established for any given patient. The proper administration of iCSTs should reduce the reactivity of hyper-reactive airways in the asthmatic patient. In turn, the absence of reactivity should be reflected in a lower number of asthma exacerbations, and minimisation of quantity of health services used. Optimal control results in 'the' lowest level of

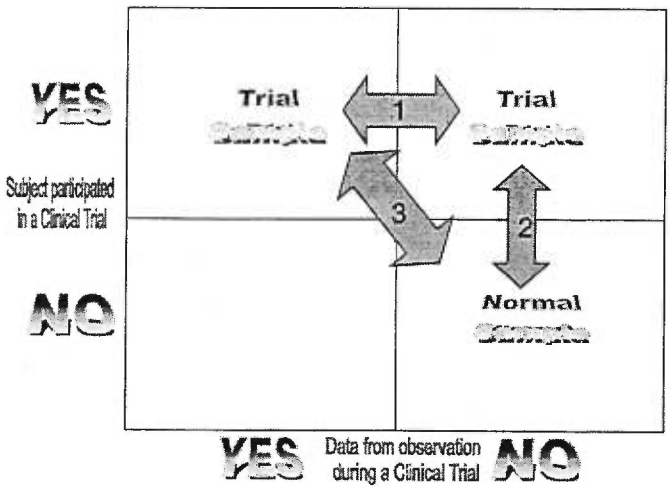
health services use. Such level of use can be measured by its cost: tallying the number of units used at an accepted price. In pharmacoeconomic terms, this would be the direct costs of the asthma treatment for the subject.

The control of the disease by iCST therapy is subject to various influences (factors) resulting in an actual control which may be less than optimal. Differences between optimal and actual control should be measurable in terms of the direct costs consisting of the resources used other than iCSTs, including the other anti-asthma medications, physician visits, emergency care services, and hospital stays.

As discussed in the review of the factors which influence the use of health resources (Chapter 2), the construct of the subject, the treatment, the setting and the observation will influence use and cost of resources. Therefore, we wanted to examine the influence of the construct differences between the clinical trial and the normal clinical setting on the use and cost of resources. The differences due to the protocol which will be examined in the following three chapters (Chapters 5 to 7) are a combination of aspects of the setting, subject and treatment constructs, and will be looked at in two groups of asthmatic subjects in trial and non-trial settings.

The schematic diagram in Figure 4.1 summarises the comparisons being made.

Figure 4.1 Influence of the randomised clinical trial setting on the use and cost of health services in asthma: the 3 comparisons made



The first comparison will look at the use of resources in subjects during and outside of the clinical trial period. This will allow us to explore the influence of the setting and treatment associated with the RCT protocol, combined with the 'Hawthorne effect'. The second comparison will look at the use of resources in subjects who had been selected for RCT participation and those who had never been so selected. This will allow us to explore the differences caused mostly by the subject construct (such as the learning experience of the RCT and the various criteria for inclusion in the RCT), as well as aspects of the treatment construct (having been treated by health professionals involved in RCTs). The third comparison explores all the differences combined.

To explore the influence of the difference in constructs two groups of subjects were recruited: subjects who had participated in an RCT (TS) and subjects who had not (NS).

Companies marketing inhaled corticosteroids and hospital-based clinical trial research groups working in the field of asthma in Quebec were contacted and asked to identify all the RCTs which 1) recruited adult asthmatic patients and required the use of iCSTs in at least one arm of the trial, 2) were completed in Quebec between January 1, 1990 and March of 1997, and 3) were of a duration not less than 8 weeks (including the run-in period). The list of trials is found in Table 4.1. The subjects who had taken an iCST during these trials were identified. An attempt was made to contact each individual and obtain their consent to participate and allow release of their pharmacy records.

We tallied the direct costs which would have been measured during the course of clinical trials as if a cost-efficacy study had been commissioned alongside the trial, and compared these to the direct costs which were incurred during normal, non-trial conditions.

Table 4.1 List of clinical trials from which clinical trial subjects were recruited

No	Year	Design	Length (weeks)	Subjects N=154 (71)	Inclusion criteria	Main exclusion criteria	Asthma Rx
1	1993-1994	RCT* parallel comparing two bronchodilators	24	7 (3)	• >=18 years old • user of iCSTs† • FEV_1 >=40% pred & >=1.0 L • Reversability ‡ >= 15%	• > 20 pack-years of smoking history • other lung diseases • regular oral steroid treatment	• continued iCSTs as before study • use beta-2 agonist (test or control drug) twice daily
2	1991-1992	RCT crossover comparing iCST with placebo	52	16 (1)	• diagnosis of occupational asthma • offending agent removed	• oral steroids within recent 12 weeks	• continued beta-2 & theophyllines as before study • use iCST (test drug) or placebo 1000µg¶ daily
3	1995-1996	RCT crossover comparing two iCSTs	52	50 (45)	• >=18 years old • moderately severe chronic stable asthma • receiving between 1000 & 2000µg iCST per day	• current or recent smoker • use of 4 or more courses of oral steroids per year or any course within recent 12 weeks • serious uncontrolled systemic disease • recent asthma hospitalization	• discontinued beta-2 & iCSTs • rescue beta-2 provided • use iCST (test or control drug) 1000 to 2000µg daily
4	1991	Open-label RCT crossover	30	33 (9)	• mild to moderate asthma • receiving minimum dose of iCSTs		• continued beta-2 & theophyllines as before study • use iCST in two different dosage regimens

Table 4.1 continued

No	Year	Design	Length (weeks)	Subjects N=154 (75)	Inclusion criteria	Main exclusion criteria	Asthma Rx
5	1994-1995	RCT comparing two iCSTs	24	3 (2)	• 18 – 75 years • history of reversability responding to iCSTs • receiving between 1500 & 2000µg iCST per day • Reversability >= 15%	• serious uncontrolled systemic disease • recent asthma hospitalization	• discontinued beta-2 & iCSTs • rescue beta-2 provided • use iCST (test or control drug) 2000µg or 4000µg daily
6	1994-1995	RCT parallel comparing two iCSTs	12	20 (10)	• aged 12 or older • moderate asthma responding to beta-2 • receiving between 400 & 1200µg iCST per day	• use of 2 or more courses of oral steroids within recent 12 weeks • serious, unstable concurrent disease	• discontinued beta-2 & iCSTs • rescue beta-2 provided • use iCST (test or control drug) 1000µg daily
7	1991-1992	RCT comparing two iCSTs	32	14 (5)	• 18 years or over • receiving iCST • Reversability >= 15%		• discontinued beta-2 & iCSTs • rescue beta-2 provided • use iCST (test or control drug) 800µg daily
8	1992	RCT comparing iCSt and placebo	8	2 (0)	• 18 years or over • mild asthma • minimum use of beta-2		• discontinued beta-2 & iCSTs • rescue beta-2 provided • use iCST (test drug) or placebo

The number of subjects listed are first those who were recruited for the study. The number in brackets is those for whom all information on anti-asthma health services use is available for at least a portion of the data collection period.

* RCT = Randomized controlled trial blinded for treatment received

† iCSTs=inhaled corticosteroids

‡ Reversability = change in the FEV_1 , generally after 15 minutes after administration of bronchodilator

¶ Quantity of iCSTs are expressed in beclomethasone equivalents of 1 beclomethasone = 0.5 fluticasone = 0.8 budesonide.

The letters used to approach the individuals from the three hospital centres are found in Appendix 1 (French language versions) and 2 (English language versions). The potential subjects were asked to sign a consent form (Appendix 3 and 4). The clinical trial files for the recruited individuals were then searched and the use of health services for asthma were extracted using a collection form (Appendix 5). Individuals were asked to name their pharmacists from whom they purchased their anti-asthma medication prescriptions. The pharmacists named in the consent form were then contacted and asked to supply details of the anti-asthma medications dispensed and complete the medications collection form (Appendix 6). Use of physician visits and hospital stays were supplied for these individuals by the RAMQ and MSSS.

The use of asthma-related health services during the time of the trial (trial period) and a period immediately adjacent to the trial (non-trial period) were recorded and a cost was attributed using the methods detailed in Chapter 5. The comparison of the two time periods enabled us to look at how, in the same individual, the constructs of the trial affect the use of health services and the measure of direct costs. The results of these comparisons are the subject of the article which forms Chapter 5.

The second group (NS) were asthmatics recruited in the community who had never participated in a clinical trial, and we measured their use of asthma

related health services and the direct costs in the same way that these were measured in the TS. They were recruited by their community pharmacists. The pharmacists verified the subject's use anti-asthma medication from their patient records (Appendix 7) and then asked their patients a series of questions to determine eligibility (Appendices 8 and 9). Patients were asked to complete a consent form (Appendices 10 and 11). Their prescription medication use was collected using the same form used for the TS (Appendix 5). The instructions for the pharmacist were set forth in a short letter (Appendix 12).

The comparison of the use of health services and the direct costs of asthma treatment in these two groups, controlling for differences of age, gender and the like, allow us to see how being chosen as a subject, and having participated in a trial, influences the use and cost of health services. The results of this comparison are reported in the article found as Chapter 6.

In Chapter 7, the use and cost of health services measured in the TS during the trial period is compared to the use and cost measured in the NS, controlling again for those independent variables which were seen to significantly influence the outcome. This chapter addresses the question of how the trial measurement relates to the real life measurement, when both the subjects and the setting differ. Aspects of the construct validity of the clinical trial are discussed in the light of these findings.

In addition, in Chapter 7, an estimate of the cost of asthma in the average Canadian adult asthmatic in the real life setting is estimated, based on the measurement in our two samples. This is compared to what would have been generalised from the clinical trial setting.

Details of the methodologies used are found in the relevant chapters. The comparison of the TS' use and cost of health services during and outside the period of the RCT included: proportions of users/non-users of categories of services; average daily quantities of iCSTs and short-term bronchodilators; and annual quantities and cost of total anti-asthma health services and categories of those services. Comparisons were done using two-related samples or paired data tests. Outcome variables were first grouped into categories, and the influence of certain independent variables was explored using Chi-square.

The influence of group (TS vs. NS) on the use and cost of health services outside the period of the RCT was tested mainly by regression analysis. We had small sample sizes, so did not attempt to remove any outliers. After testing for normal distribution, non-normally distributed variables were either transformed into base 10 Log, or if there was two-modal distribution, they were reclassified as categorial variables. Simple and multiple linear least-squares regression analyses or logistic regression analyses were used. The same

methodology was used to compare costs of asthma-related health services in the TS during the trial period to the NS.

Because this was an exploratory study, the level of statistical significance used for the α was 0.15, and confidence intervals of 85% were used to determine whether the predictive power of the independent variables differed between settings or groups.

The health services measures used were not expressly validated for this study. We assumed the validity of the use of services information recorded in the RCT files, although certain studies have cast doubt on the accuracy of the information reported by some RCT subjects (Mawhinney et al., 1991; Rand et al., 1992). Pharmacy records were used as a proxy for prescription medication use. The MEDECHO data base of the MSSS which contains information on the hospitalisations used was validated for the diagnosis of asthma at 95% (Delfino et al., 1993). Finally, the RAMQ data base for physician visits is currently being validated by Tamblyn and colleagues (personal communication), and we did not rely on the diagnosis in this data base for our study.

The main outcome of interest in the three comparisons is costs of asthma-related health services. Two main elements comprise these total asthma-related health services costs: the cost of the asthma treatment itself (in this

case the iCST) and the costs associated with the consequences of the treatment, which include the costs to control the asthma and its symptoms, and the costs of monitoring the patient and the progress of the disease. We therefore made a distinction between the costs of the iCST and the rest of the total costs, and analysed the latter separately as representing the costs of the consequences of treatment with iCST.

Chapter 5

Cost-efficacy vs. cost-effectiveness: Can we generalize costs of health services from the clinical trial setting to real life?

The following article is being submitted for publication to *Medical Decision Making.*

Cost-efficacy vs. cost-effectiveness: Can we generalize costs of health services from the clinical trial setting to real life?

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ABSTRACT

This study explores the external validity of the clinical trial (RCT) with respect to the use and cost of asthma-related health services: anti-asthma medications, ambulatory physician services, asthma hospitalisations and

emergency room services. For the trial period (TP), these services were estimated in 71 subjects (for whom all information was available) who had participated in an RCT involving inhaled corticosteroids (iCSTs) and compared, using non-parametric tests for paired data, to those during a non-trial period (NTP) immediately adjacent. Average overall costs were estimated at $922 per year for TP, higher than NTP ($827, $p<0.01$). Also higher during TP was daily iCST use (1232 vs. 507 µg per day). Ambulatory physician use and short-term bronchodilator use were higher during NTP. The RCT outcome of use and cost of health services is likely the result of a combination of the iCST, the circumstances of the RCT and an interaction of the two which makes generalisation difficult.

Key words: Economic evaluation, asthma, cost-effectiveness, drug therapy, inhaled corticosteroids, external validity

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INTRODUCTION

The measurement of the effect of treatments in health care is largely based upon the results of randomised clinical trials (RCTs). The internal validity of the RCT is generally recognised, but many questions have been raised as to its external validity (1-3). For example, RCT results can be generalised only to the extent that the indications in 'real life' are similar to those of the trial. But there have been differences demonstrated between the indications seen under normal clinical conditions and the indications approved by the FDA (4). In addition, subjects of an RCT are likely to be more compliant. Compliance to inhaled corticosteroid (iCST) therapy during an RCT is better than under normal conditions, particularly if the trial is short-term (5). This may be accentuated in a complicated therapeutic regimen. Fewer medications were seen in an HIV non-trial group than in a trial group (3).

This problem of external validity of the RCT is especially important when the measure targeted is the economic impact of the intervention (6,7). The economic impact is most crucial to those making decisions of forecasting and budgeting in relatively large heterogenous populations under conditions of normal use over relatively long periods of time. These circumstances are generally not found in the controlled clinical trial, which is usually of short duration, in a sample of homogenous subjects, and under carefully monitored conditions.

The question of the generalisability of the results of the RCT has been seen as a question of its external, or construct validity, which can be categorised as constructs of the sample, the treatment, the observations and the setting (7,8). It is generally well known that differences in the demographic characteristics of the subject construct, as well as their compliance behaviours will affect the results of the RCT (1,6,9). The authors wished to explore the influence of the other constructs on the use of health services. The example of the treatment of asthma by iCSTs was chosen as a pilot study.

Because iCSTs are antiinflammatories which, when properly administered, reduce the reactivity of hyper-reactive airways in asthmatic patients, (10,11) their correct use should result in the minimum utilisation of alternative anti-inflammatory treatment such as oral steroids, and rescue-type health services, such as beta-2 agonists (12), emergency care visits and hospitalisations. These have been included as study outcomes (end-points) in inhaled steroid trials (13-16), in economic evaluations of asthma medications (17-27), and in evaluations of asthma education and monitoring programs (28-32). Both use and cost of such services can serve, and have been used, as trial outcomes. For the purpose of cost-effectiveness ratios, however, care must be taken to not duplicate measures in both numerator and denominator, so cost-effectiveness ratios must use an effect outcome which has not been incorporated as a cost.

The treatment construct of the RCT will likely differ from the treatment in real life, and this will have a measurable impact on the use of resources and their cost. As explored in the case study, the RCT treatment constitutes not only iCST use, but the delivery of the treatment including the professional expertise and accessibility of the health professionals providing that treatment. The quantity of medications to be taken in any RCT is generally detailed in the trial protocol, and we should see a larger variation in real life treatment than in RCT treatment due just to this factor.

The setting of the RCT, with its provision of free medications should also have an influence. Finally, the subjects' behaviour is likely to be different in the RCT than in real life, simply because he or she is in a trial situation (the Hawthorne effect[1]). All these should combine to impair the external validity of the trial insofar as the measure of use and costs of health services are concerned, even if the individual subject remains constant. The outcome effect of the RCT as measured by the use and cost of health services is a result of the iCST treatment, the other factors which constitute the RCT construct, and their interaction.

It was to explore the capacity to generalise the costs measured under RCT conditions to 'real life' that this study was conducted. The differences in the

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[1] There was a study conducted in the Hawthorne Works of the Western Electric Company, intended to measure the effect of lighting levels on the productivity of the workforce. The results of the study showed a positive impact of all the lighting levels (Roethlisberger et al., 1961).

use of asthma-related health services in a group of asthmatic subjects taking iCSTs under RCT conditions were measured and compared to the use of the same services in those subjects under non-trial conditions. In addition, we also explored the influence of various characteristics of individuals on cost and use, and the direction and the extent of the influence of those characteristics in the RCT and the normal setting.

METHODS

Subjects. Companies marketing inhaled corticosteroids and hospital-based clinical trial research groups working in the field of asthma in Quebec were contacted and asked to identify all the RCTs which 1) recruited adult asthmatic patients and required the use of iCSTs in at least one arm of the trial, 2) were completed in Quebec between January 1, 1990 and March of 1997, and 3) were of a duration not less than 8 weeks (including the run-in period). The subjects who had taken an iCST during these trials were identified. An attempt was made to contact each individual and obtain their consent to participate and allow release of their pharmacy records.

Data Collection. The subjects' use of health services was collected for the period of the clinical trial during which they were taking an iCST (trial period--TP), and a maximum period of 6 months immediately following or preceding that TP (non-trial period--NTP). Use of health services consisted of 1) the

anti-asthma prescription medications dispensed to the subject, 2) their consultation with family practitioners, pneumologists or internal medicine specialists, and 3) their hospitalisations with a recorded diagnosis of asthma. The presence of major comorbidities and the severity of asthma was estimated from notes in the clinical trial admission forms. Those prescribed 1000µg or less per day of iCST equivalent to beclomethasone were deemed to have mild to moderate asthma, and those prescribed higher were deemed severe.[2] None of the subjects were classified as having very severe asthma; uncontrolled or very severe asthma were exclusion criteria for all the studies included. Major comorbidities were coded if there was noted presence of heart disease, hypertension, nephritis or thyroid problems.[3]

Prescription drug services were collected from all of the individual pharmacies identified by the recruited subjects. The subjects had been asked to provide the names and addresses of all pharmacies from which they purchased anti-asthma medication. Details of prescriptions dispensed for iCSTs, bronchodilators, theophyllines, oral corticosteroids, and antibiotics were collected, and use or non-use of other major classes of medications were noted. The type and quantity of medications subjects received as part of the trial protocol were collected from clinical trial files. This allowed the inclusion of the medications which had been provided by the trial sponsor.

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[2] Those prescribed beclomethasone 1000mcg equivalent with additional long-term bronchodilators were deemed severe.

[3] Minor comorbidities noted in the files were allergies, rhinitis, arthritis, minor gastro-intestinal problems, hypercholesteremia, ulcer, back pain, and the like.

Physician consultation information was obtained from the RAMQ who manage the data banks of the government-funded provincial health insurance program, and hospitalisation information from the provincial ministry of health. Physician visits were not restricted to any particular diagnosis, as the validity of the diagnosis in this type of data base has not been ascertained for the specific services delivered (32,33).[4] The type of physician deemed as the major caregiver for each subject was determined by the majority of visits (generalist or specialist), and when there were no physician visits charged, it was assumed to be a specialist.

Costs for drug use consisted of the purchase price per unit dispensed as listed in the January 1996 list for the public insurance plan, together with a 6.5% wholesale upcharge, and a pharmacy service fee of $7.77 per prescription dispensed.[5] A per-dose cost for drug use during clinical trials was attributed using the same prices.[6] Hospitalisation costs consisted of hospital-based physician visits and all hospital days with a principal diagnosis of

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[4] We would not be using the diagnosis here to determine whether the subject has a particular health problem or not (diagnoses in these types of data banks have been used to identify subjects with a particular problem), but to determine if the service had been delivered for that health problem. The visit to the physician could have been for the subject's asthma, or other health problems which were not related to asthma. Without a chart review, it is difficult to determine the association of the diagnosis with the service.

[5] The service fee of $7.77 is the average dispensing fee reported for 1996 by the Quebec pharmacy owners association (AQPP). There was one compounded prescription dispensed with a fee of $11.12 (average compounding fee from personal communication with AQPP). The cost of the ingredients was based upon the January 1996 list.

[6] One of the clinical trials recorded use of a 500 mcg strength of fluticasone (not marketed), and the price per puff was calculated as twice that of the listed price of the 250mcg strength.

asthma. A per diem hospital stay cost ($517) was estimated using the per diem for Sacré-Cœur Hospital from the 1996-97 financial report of the Quebec Ministry of Health for hospital services. The cost of physician visits (emergency, inpatient and outpatient) was calculated using fees in vigour for 1996 from the universal health insurance plan. Emergency services cost consisted of hospital emergency department-based physician visits and a per-episode cost. The cost of emergency episodes ($128) was estimated using the 1995-96 per patient-visit cost of emergency room visits for Sacré-Cœur hospital. Total asthma-related costs consisted of the costs of anti-asthma medications, costs of hospitalisation, costs of physician ambulatory visits and costs of emergency room episodes.

Data Analysis. Variables of use/non use of categories of services were created to look at proportions of users/non-users. Quantities of iCSTs and short-term bronchodilators were calculated on a per diem basis, by averaging the quantity dispensed during the measured period over the number of days in that period. All other quantities and cost of services were estimated on an annual basis, by dividing the quantity or the cost during the measured period by the number of days during that period, then multiplying the daily average by 365.

Data for the TP and NTP were compared using SPSS for Windows version 7.5.1. The composition characteristics (e.g., age group and gender) of the

overall sample and subsamples were compared using StatXact-3 version 3.02.

Because this was an exploratory study and the observation of tendencies and directions of changes in use were the main outcomes of interest, an α of .15 was used as the threshold for differences in most cases. Differences in sample proportions were measured by McNemar's two-related samples test. Mean use and cost of health services during the trial and NTP were compared using Mann-Whitney (Wilcoxon) tests.

The influence of the trial setting on the variations in use of anti-asthma medications, physician visits and the cost of asthma-related health resources use was explored using a Chi-square test in the subset of the recruited subjects for whom all resource use information was available. Outcome variables were first grouped into categories. The influence of certain independent variables: severity of asthma, presence of major comorbidities, type of physician and average daily dose of iCST on the outcome variables was explored. Confidence intervals of 85% were used to determine whether the predictive power of the independent variables differed from one setting to another.

RESULTS

Two pharmaceutical manufacturers and respirologists from 3 research groups identified a total of 8 studies meeting the inclusion criteria. These studies recruited subjects in either Montreal or Quebec City, or both. 254 individuals who had been taking inhaled corticosteroids were identified. They were contacted by letter, followed by a telephone call to those individuals who did not respond. For those who could not be contacted by telephone, RAMQ provided a recent address. A second letter was sent to the new address. Only 9 subjects actively refused to participate in the study, 14 subjects could not be found in Quebec, 52 subjects did not return the signed consent form, and 10 consent forms were incomplete. Of the 158 subjects recruited, four had clinical trial dossiers which we were unable to locate, leaving 154 subjects in the Trial Sample, 84 in Montreal and 70 in Quebec. The description of the recruited subjects is found in Table 1.

There were 71 of the subjects for whom we had complete health services use information from all sources and for both the TP and the NTP. Several analyses using particular types of services could be done with a greater number of subjects, but the overall cost comparisons and drug use comparisons were limited to that number.

Table 1 Description of recruited subjects

	Recruited sample N=154		Subset with pharmacy data N=75		Corr. p-value*	
	n	%	n	%		
Gender					0.96	
Male	57	37.0	28	37.3		
Female	97	63.0	47	62.7		
Age group (years)						
20 to 44	56	36.4	28	37.3	0.93	
45 to 59	52	33.8	24	32.0		
60 and over	46	29.9	23	30.7		
Asthma severity					0.10	
Mild/moderate	67	43.5	24	32.0		
Severe	87	56.5	51	68.0		
Comorbidities (major)					0.83	
None	139	90.3	67	89.3		
One or more	15	9.7	8	10.7		
Location					0.46	
Montreal	84	54.5	37	49.3		
Quebec	70	45.5	38	50.7		
Overall	154	100	75	100		

* Pearsons Product-moment correlation. (StatXact) Two-sided asymptotic p-value for testing no association.

Information on hospitalisations and use of physician services (fee-for-service visits, consultations or examinations by general practitioners, respirologists or internal medicine specialists) were obtained for all but one subject. Although all subjects identified their pharmacies, many pharmacies keep records for no longer than 2 years. The periodic purging of electronic patient records in pharmacies meant that about half of the subjects could not be included in the analyses of overall and drug services use. Information on use of ambulatory pharmacy services was obtained for 75 of the 154 subjects. Table 1 includes the description of this subgroup. Few significant differences were seen in the

subgroup with respect to the overall group, although the pharmacy subgroup was seen to have a higher proportion of severe asthmatics, and a higher proportion of individuals with one or more major comorbidities.[7] For four subjects, the data for ambulatory drug use during the TP was incomplete and these subjects were not included in this part of the analysis. This resulted in a total of 71 subjects with complete asthma service use information.

The data collection periods were an average of 190 (SD=119) days for the TP, and 181 (SD=7) for the NTP. [8] Overall, for 115 (75%) of the subjects non-trial use was measured after the TP; of the 71 subjects with complete pharmacy use information, it was measured after for 42 (59%).[9] Comparisons of proportion, quantity and cost of use of different services revealed no significant differences between the groups as a function of this time-frame, with the exception of the cost of hospitalisations which was significantly higher (p=.03) when the period measured fell prior to the TP.

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[7] The total group (n=154) was also compared to the subgroup with the non-trial period following the trial period (n=42). Using Pearson's product-moment correlation coefficient, agegroup, gender, and city were all independant (p<.15) (Pearson's R=<-.01, <-.01, and .05, respectively) and severity of asthma and the presence of comorbidities were significantly different (Pearson's R=.11 and .13).

[8] For most subjects, the collection period was 6 months. However, it was shorter if the December 1, 1996 fell before the end of the 6 month period following the end of the clinical trial, and was also shorter if the beginning of the pharmacy data collection period (the start date when the pharmacy anti-asthma medication records were available) was after the theoretical start date of the collection period.

[9] The total group (n=75) was compared to the group with the non-trial period following the trial period (n=42). Using Pearson's product-moment correlation coefficient, agegroup, gender, severity of asthma, and city were all independant (p=0.84, 0.74, 0.69, and 0.19, respectively) and the presence of comorbidities was significant (p=0.09).

Results pertaining to use and cost of anti-asthma medications are found in Table 2. The proportions of subjects which had at least one recorded use of particular medication groups during the TP and NTP were relatively constant for long-acting bronchodilators, oral corticosteroids and theophyllines, but were lower for iCSTs and short-acting bronchodilators, and higher for antibiotics.

Table 2 Anti-asthma medication use, trial period and non-trial period: percentage of users of one or more medication groups, average quantities and costs

	Trial Period N=71	Non-Trial Period N=71	
	%	%	p=*
Proportion users of:			
Any antiasthmatic	100	85.9	<.01
Inhaled Corticosteroids	100	69.0	<.01
Short-acting Beta-2s	90.1	64.8	<.01
Long-acting Beta-2s	16.9	16.9	1
Oral Corticosteroids	15.5	16.9	1
Theophyllines	1.4	0	1
Antibiotics	11.3	25.4	0.06
Average daily quantity of:	*Mean(SD)*	*Mean(SD)*	*p=***
Inhaled Corticosteroids (µg)	1232(472)	507(534)	<.01
Short-acting Beta-2s (puffs)	1.17(1.89)	2.09(2.39)	<.01
Average annual cost of:			
Inhaled Corticosteroids	$642.23 (275.14)	$287.54 (300.56)	<.01
Other anti-asthma med	$151.69 (216.14)	$157.14 (166.45)	0.22
Any anti-asthma med	$793.91 (387.33)	$444.68 (405.31)	<.01

* McNemar's two-related samples test
** Mann-Whitney (Wilcoxon) test

There were also significant differences in the average daily quantities of measured medications: average daily use during the TP of iCSTs was 1232µg, more than double that of the NTP which was 507µg. Use of short-term bronchodilators was lower during the TP at 1.2 puffs per day, almost half

of that during the NTP, 2.1 puffs. The significant difference is maintained when the use of iCSTs are measured in cost terms. There was, however, no significant difference between the cost of all anti-asthma medications other than iCSTs. This could be due to substition of one type of treatment for another, as we did see differences in quantities of some of the specific items, such as antibiotics and short-acting bronchodilators. The overall costs were largely accounted for by the iCSTs, so the costs of all anti-asthma medications during the TP were estimated to be significantly higher than those during the NTP.

The summary results of physician services and comparisons are found in Table 3. Physician visits were categorised according to the type of practitioner and the location of the service billed. As most of the visits to specialists were to pneumologists (there were only 7 internal medicine specialist visits) the specialist visits were grouped together. All visits except those made in emergency and hospital inpatient settings were regrouped as total ambulatory services. During the periods searched (TP and NTP together), there were physician visits made to either family practitioners or specialists by 88.9% of the sample, and the proportion of the sample having one or more physician visits was higher during the NTP than during the TP. This difference is still significant when the physician visits were grouped by type of speciality. When categories of specific visit groups were examined by the coded location of the visit, there was no difference seen between the two

periods for emergency room or hospital-based visits, but a higher proportion of the sample had one or more ambulatory visits during the NTP. The number and cost of visits was also higher overall during the NTP, and this was true for most sub-groups.

Table 3 Physician use, trial period and non-trial period: percentage of users of one or more physician visits, average quantities and costs

	Trial Period N=153	Non-Trial Period N=153	
Proportion users of:	%	%	p=*
General practitioner	59.5	69.9	0.04
Specialists	17.0	63.4	<.01
Emergency visits	12.4	14.4	.71
Total Ambulatory	63.4	86.9	<.01
Any type of visit	65.4	88.9	<.01
Average annual quantity of:	*Mean(SD)*	*Mean(SD)*	*p=***
General practitioner	3.91 (6.02)	4.81 (7.75)	.08
Specialists	0.55 (1.65)	1.98 (2.20)	<.01
Emergency visits	0.42 (1.32)	0.89 (3.18)	.12
Total Ambulatory	4.00 (5.89)	5.47 (5.74)	<.01
Average annual cost of:			
General practitioner	$82.23 (115.79)	$104.96 (179.35)	.07
Specialists	$17.15 (51.49)	$65.55 (78.43)	<.01
Emergency visits	$6.71 (22.36)	$14.83 (55.85)	.16
Hospital visits	$1.49 (15.97)	$15.44 (82.80)	.03
Total Ambulatory	$92.19 (117.44)	$142.27 (148.51)	<.01

* McNemar's two-related samples test
** Mann-Whitney (Wilcoxon) test

The proportion of subjects with one or more hospitalisations with a principal diagnosis of asthma was very low: there were no hospitalisations during the TP, and only 3 individuals so hospitalised during the NTP.

Table 4 summarises the overall costs for the two periods for the subgroup of subjects with complete information. Average annual costs for hospitalisation

were higher during the NTP as were average annual costs for all anti-asthma health services save iCSTs. Overall costs are estimated to be higher during the TP, due to the large significant difference in the estimated cost of anti-asthma medications. Although there were no asthma hospitalisations recorded for the TP, several hospital-based physician visits were reimbursed and have been included in the analysis, because diagnosis was not a variable retained from the physician services data bank.

Table 4 Average annual costs of antiasthma medications, emergency room visits, ambulatory physician visits, hospitalisations and total costs, trial period and non-trial period

Average annual cost of:	Trial Period N=71	Non-Trial Period N=71	p=*
Ambulatory physician visits	$89.82 (116.72)	$150.06 (166.80)	<.01
Anti-asthma medications	$793.91 (387.33)	$444.68 (405.31)	<.01
Emergency department	$35.26 (113.28)	$69.85 (181.04)	.21
Asthma hospitalisation	$2.75 (23.25)	$162.64 (977.59)	.14
Total costs except for iCSTs	*$279.52 (282.98)*	*$540.95 (1079.11)*	*<.01*
Total costs	*$921.74 (433.19)*	*$827.23 (1153.16)*	*<.01*

* Mann-Whitney (Wilcoxon) test

Total costs were broken down into 2 categories: low (up to $599) and high ($600 or more). Total costs exclusive of iCSTs (Non-iCST costs) were categorised as low (up to $299) and high ($300 or more). Ambulatory physician visit costs were also categorised as low (up to $99), and high ($100 or more). Anti-asthma medication costs were categorised as low (up to $599) and high ($600 or more). The cut-off points were created close to the median values of the variables, for a relatively even distribution in the categories.

In general, high vs. low costs differed significantly (Chi-square Fisher Exact Test) from the TP to the NTP. A large proportion of the group (44%) who were seen to have low total costs during the NTP had high total costs during the TP. The same trend was seen for anti-asthma medication costs. However, the opposite is true when non-iCST costs and physician costs are examined.

There is a large group of subjects having high non-trial physician costs and low physician costs in the TP (34%), a rather small group showed the opposite tendency (7%). (Fisher Exact test: $p=0.04$).

There is a tendency for the subjects having low NTP anti-asthmatic costs to have higher TP anti-asthmatic costs, and this represents 31% of the sample. Only 1 individual showed the opposite trend. (Fisher Exact: $p<0.01$).

A supplemental analysis was conducted using 3 categories of costs in each of these output variables, and the results were in the same direction, if not always significant. [10]

When all the comparisons are taken together, the expected result with respect to variation in the use and cost of health services was seen: in almost every

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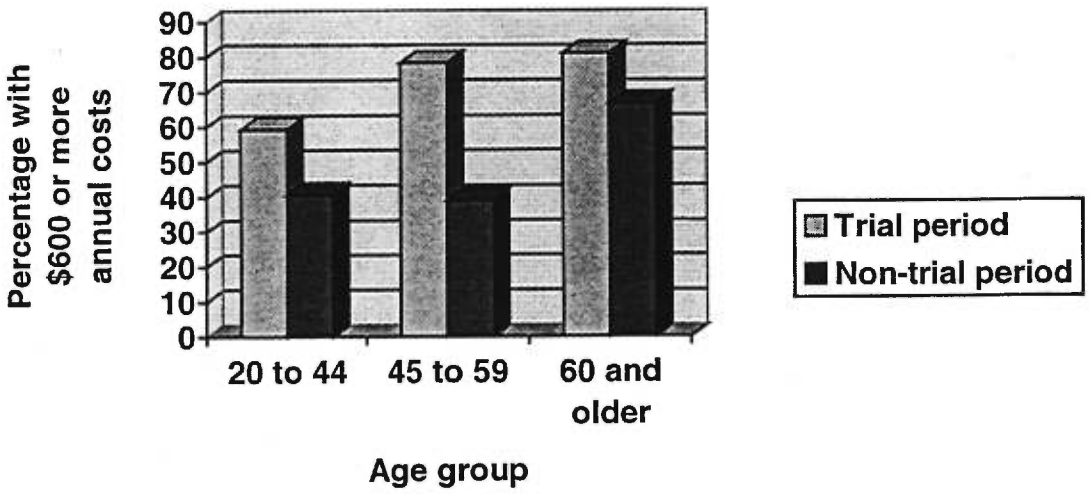
[10] Comparison of the cost of anti-asthmatic medications was not significant ($p=0.81$). The total cost and cost of physician ambulatory services were ($p<0.01$).

case, the NTP measure showed greater variation than the TP measure (Tables 2, 3 & 4). The only exception was total ambulatory physician visits, which was almost identical.

The significance of age group, gender, asthma severity, physician type, city, average inhaled corticosteroid dose and presence of major comorbidities on the total cost was explored.

Figure 1 Influence of age group on total costs, trial period, non-trial period



Total costs (Figure 1) significantly (p=0.12) differed according to age group only during the NTP, with the older (60+) age groups having a higher proportion of individuals with higher costs (67% vs. 41% in the under 45 and 39% in the others). During the TP there is no significant difference (p=0.18).

Women were seen to be significantly more present (57% vs. 33% of men) in the higher total cost group during the NTP (p=0.09), but no difference was seen during the TP (p=0.28).

Physician type (specialist vs. general practitioner) did not significantly influence cost category during the TP (p=0.61), nor the NTP (p=0.16) .

A high average daily dose of iCSTs was significantly associated with higher total costs only during the NTP (p<0.01). There was little variation in daily dose during the TP, and a low probability of association with cost differences (p=0.64).

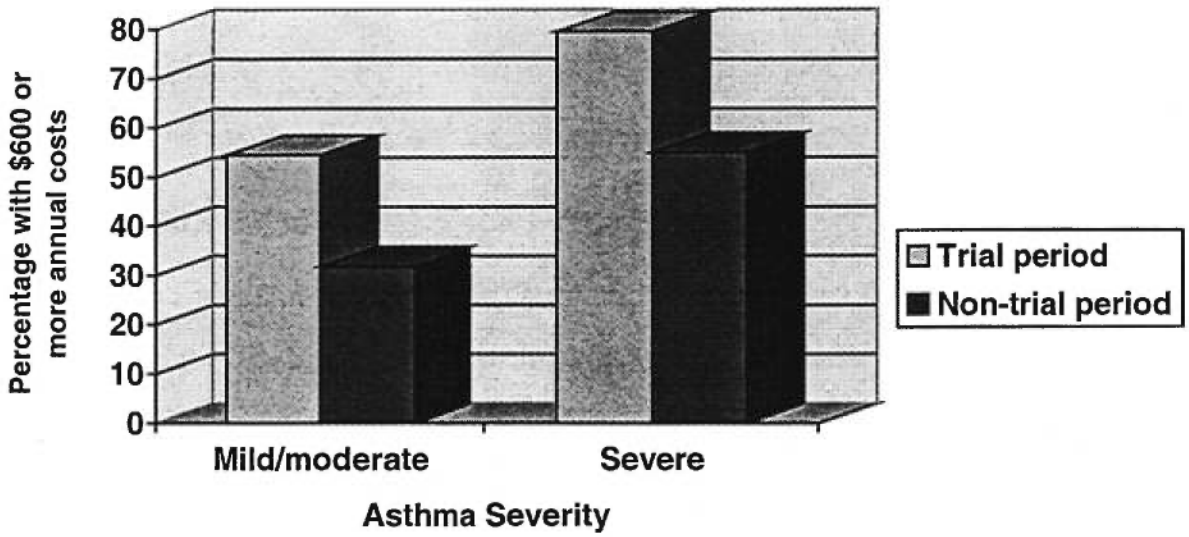
The location of the clinical trial (and the subjects enrolled) had a significant influence on total cost, both during the TP (p<0.01) and the NTP (p<0.01). For both periods, Montreal is associated with higher costs; Quebec city with lower costs. The variable of city was explored further to see if there were other variables which could explain this difference, and it was found to be highly correlated with most of the other variables: age group (p=0.02), gender (p=0.03), type of physician (p<0.01), inhaled corticosteroid dose (trial and non-trial) (p<0.01), and asthma severity (p=0.05).

Severity of asthma had a significant influence on total costs (Figure 2) during the TP (p=0.05) and the NTP (p=0.08). Severe asthma was associated with

higher costs in both periods. There was a higher correlation between the prescribed daily dose of iCST as recorded in the clinical trial admission form and the dose as seen to be taken during the TP (Pearson correlation = 0.77) than with the dose seen to be taken during the NTP (Pearson correlation = 0.51), although both are significant ($p<0.01$).

Major comorbidities were found to have no significant influence on total costs, neither during the TP ($p=0.70$) nor the NTP ($p=0.61$). This may confirm that the services we measured are not overly related to other health problems, and that our use of all physician visits for the listed specialities has reasonably excluded services for other problems.

Figure 2 Influence of severity of asthma on total costs, trial period, non-trial period



Again, in a supplemental analysis using 3 categories of total costs, the results were in the same direction, but the significance and p-values were not necessarily the same.

For each of the variables age group, gender, type of treating physician and iCST dose, the significance of the association with overall costs is all increased from the trial to the NTP. For severity of asthma there is little change in significance.

DISCUSSION

This study shows that there is a significantly higher overall cost of anti-asthma therapy in the clinical trial setting than in the normal setting in a group of relatively stable, mild-to-severe asthmatics. The reason is that most important component is iCST cost, which is significantly higher in the trial setting. However, the total costs of anti-asthma therapy net of the costs of iCSTs were significantly higher in the normal setting. We could be seeing the effect of substitution of other resources for iCSTs. Cost exclusive of the treatment under investigation and cost of treatment represent two distinct categories of cost. The cost component of cost-effectiveness ratio outcome in trials have sometimes been expressed as one of these, sometimes as the other. Therefore, it was important to look at both these measures.

With respect to specific categories of quantity and cost, there are also important differences. Treatment is different in the two settings. In anti-asthma drug use, not only is the variance much higher in the normal setting, the trial setting sees double the average daily dose of iCST as the normal setting. The level of adherence to treatment could be a factor here. Another explanation could be that iCST dose in trial protocols are higher than needed for adequate control, to ensure that anti-inflammatory effects are felt.

Other components of the treatment package are also very different. The trial setting sees a higher proportion of users of short-term bronchodilators, but a lower average daily dose than the normal setting. The use of rescue medications such as short-term bronchodilators are also often seen as an outcome measure in trials, reflecting lack of control or effect of the anti-inflammatory iCSTs. We saw a difference in quantities measured of these medications, but their relatively low cost when compared to other components of the treatment mean this difference is not reflected in overall cost of medications. An alternative explanation is the substitution of one type of rescue medication for another, which again would be lost in the total cost measurement.

The trial setting also apparently reduces the need to see a treating physician—the trial subject probably feels sufficiently medically supervised by the trial process. This is true for both general practitioners and specialists,

and is reflected in the higher costs of ambulatory physician care in the normal setting. These differences in the treatment construct illustrate the difficulties of generalising RCT results.

Although the methods of recording iCSTs and rescue bronchodilators during the trial (subject reported use) and NTP (medications purchased) are not identical, the direction and significance of the differences in the quantities used seen between the two periods should nonetheless be considered useful. There is probably not a consistent under- or over-estimation of the use in the NTP from purchase to reported use: iCST use was seen to be lower in the NTP than in the TP, whereas bronchodilator use is higher.

With respect to the use of iCSTs, the significantly higher average daily dose measured during the TP could be due to a higher level of compliance than seen in normal clinical use. It could also simply be better iCST treatment during the TP than the NTP. Again, the RCT treatment construct is very different from treatment in real life.

As an aside, the review of the pharmacy records in this study revealed several of the clinical trial subjects purchasing, during the TP, medications which were to be supplied only by the study investigation group (both rescue bronchodilators and iCSTs). Although the purchase is not proof these

medications were used, it is likely.[11] Higher compliance in the trial situation does not mean perfect compliance: our observation is consistent with the literature which points out problems in compliance to trial medication (36,37).

Severity of asthma was measured by a proxy of the prescribed dose of anti-asthma medications. A combined measure of reversibility, percentage of expected lung capacity and medication use (38) was not used because all the required information was available for only 125 of the subjects. However, severity by prescribed drug only correlated (albeit mildly) with a combined measure (inspired by the tri-part score recommended (38) for use in determining the degree of disability of the disease) for those 125 subjects. [12]

It may be expected that participation in a clinical trial would have an influence on improving compliance in the subjects after the completion in the trial. If this is the case, there should be 'better' use of health services[13] seen in the group for which non-trial use was measured subsequent to the trial, than in those in which it was measured before. That was only true for hospitalisations, which were very limited in number. However, according to the clinical investigators of

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[11] These were not included in the average daily doses during the trial. Only those anti-asthma medications which were not discontinued according to the trial protocol were included from the ambulatory pharmacy records. Although including those purchased medications may have given a more complete picture of the medications the individual actually took during the clinical trial, the investigator would have had no way of knowing these medications had been used, and the resources would not have been recorded. The purpose of this study was to compare what would have been seen in resources use from the clinical trial during the clinical trial period, therefore these medications were not included.

[12] Pearson = .38, $p<0.01$, $n=125$

[13] 'Better use' here means higher quantities of iCST, and lower quantities of other services, such as short-term bronchodilators, physician services and hospitalisations.

the original trials, most of the subjects recruited in the trials had been enrolled in previous trials, so we did not have a group of 'naïve' trial subjects. This should mean that any improved compliance behaviours learned from having participated in an RCT would be present in the majority of the group. In addition, when the same series of analyses on overall costs was conducted in the group for which the non-trial data was recorded after the trial, all tendencies were the same, even if there was a certain reduction in significance (due to sample size).

The cost of iCSTs is the most important element of overall costs of asthma in this sample. This result is consistent with the recent Canadian study of the economic burden of asthma, which estimated that 40% of total direct costs of asthma were due to medication (39). Our study looks at a subgroup of mild to severe asthmatics largely taking iCSTs, so the relatively high (54%) proportion of the costs accounted for by medications during the NTP is not unreasonable. Additionally, the cost of iCSTs is proportionately much higher than the other common medication in this group, rescue bronchodilators.

The higher quantities of iCSTs used during the TP account for the high cost during this period when compared to the NTP when use was seen to be lower. The average dose received in the NTP was just under 50% of the average dose prescribed (1052μg). Certainly, if the subjects had complied more closely with the prescribed dose during the NTP, their medications cost would

have roughly doubled. This would have brought the total NTP costs to roughly $1100 (higher than the TP costs), but only if the other costs remained unaffected.

The use of rescue medication was higher during the NTP, as was the use and cost of ambulatory physician visits. Physician visits during the TP were likely lower because the individuals were followed closely by the staff of the trial investigators. The protocol-driven visits (those not included in the reimbursement records) were not included in the analysis. The follow-up procedures of the trial are part of the treatment construct which is not found in the real life situation, which accounts for the increased number of visits during the NTP. This aspect of the treatment construct of the trial makes generalisation difficult.

There is too much variation in the costs of emergency and hospital services to see significant differences between the periods, even at the very relaxed level of significance used in this study. The small sample size and six-month duration of the study period does not allow us to see the cost impact of hospitalisations, which are relatively infrequent in this group.

We used a per diem cost of hospitalisations and emergency visits in this analysis instead of actual costs. The per diem would likely have slightly over-estimated the real cost, because an asthma hospitalisation in Quebec is less

costly than the average hospitalisation (40). This underestimation is counteracted by our use of the lowest per diem of the 3 hospital sites,[14] and the result is a conservative estimate of the difference between the two periods, and a modest impact due to low frequency.

Overall costs were, in general, more affected by demographic variables during the NTP. In addition the variation in costs and quantities was greater during the NTP. This demonstrates the importance of the role of the protocol in defining the treatment construct.

Possibly the low dose of iCST used during the NTP which was seen in this group compared to the prescribed dose of iCSTs has a rather low impact on other anti-asthma costs because the prescribed dose is higher than needed for 'adequate' asthma control. This high dose may be a result of a circular relationship between low compliance rates, which cause the physician to prescribe even higher doses, assuming incorrectly that the prescribed dose is unable to control the disease, when the true reason for lack of control is low compliance. Another possibility is that the low use of iCSTs during the NTP resulted in an increase in the use of bronchodilators, a relatively low-cost impact, and not in a high-cost result such as emergency and hospital visits.

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[14] The per diem used was that of Sacré-Cœur. We had few subjects from the Montreal General Hospital, whose per diem was the highest of the three at $681. Laval was $662. These are all the per diems applicable to short-stay services. Average per visit costs for emergency departments were not available for the other two institutions.

The population studied is of course a rather narrowly defined group of well-controlled adults who have been correctly diagnosed. The overall population treated with these medications will be less uniform and these results may differ.

CONCLUSION

This study shows us how difficult it is to generalise the results of the clinical trial measure of the use and cost of health services to the non-trial situation, even when using the same individuals. Treatment and setting constructs are likely to have an important role to play in explaining the difference between the two. The research protocol, the treatment and their interaction act together to produce an effect of the RCT on the use and cost of health services which are different from that in real life.

When looking at overall anti-asthma costs in this exploratory study in a group of relatively well-controlled, mild to severe asthmatics, the trial setting is associated with higher iCST costs, and lower total costs of all other asthma related health services. The importance of the cost of iCST therapy in this population means that total overall asthma-related health costs are higher in the trial setting.

The relationship between the dose taken of iCST and the other anti-asthma health costs has been borne out by this group. In general, for the period

when the subjects are taking higher doses of iCSTs, their use of other resources to treat their disease is lower. In the non-trial period, the lower use due to poorer compliance leads to a decrease rather than an increase in total asthma-related costs because lower compliance means lower iCST costs.

Because of the difference seen, we are unable to conclude that the RCT construct is able to show us a measure of use and cost of asthma-related health services which can be translated to the non-trial situation. The effect measured in the RCT is likely a result of the iCST treatment, the trial situation itself and a combination of the two. We cannot conclude that trial situation and its interaction with the iCST treatment can be separated from the iCST treatment itself.

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REFERENCES

1. Feinstein AR. Problems, pitfalls, and opportunities in long-term randomized trials. Drug Research and Drug Development in the 21st Century, Bayer, AG Centenary Sumposium, 1988.

2. Susser M. Editorial: The tribulations of trials--intervention in communities. Am J Public Health 1995; 85:156-8.

3. Cunningham WE, Bozzette WA, Hays RD et al. Comparison of health-related quality of life in clinical trial and nonclinical trial human immunodeficiency virus-infected cohorts. Medical Care 1995;33:AS15-AS25.

4. Mak H, Johnston P et al. Prevalence of asthma and health service utilization of asthmatic children in an inner city. J Allergy & Clin Immun 1982;70:367-72.

5. Schmier JK, Leddy NK. The complexity of treatment adherence in adults with asthma: challenges and opportunities. J Asthma 1998;35:455-472.

6. Rittenhouse BE, O'Brien BJ. Threats to the validity of pharmacoeconomic analyses based on clinical trial data. Ch. 26 of Spilker B. (ed) Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd edn. Philadelphia: Lippincott-Raven Publishers, 1996.

7. Conrad KJ, Conrad KM. Reassessing validity threats in experiments. Focus on construct validity. *New Directions for Program Evaluation* 1994; 63:5-25.

8. Cronbach LJ. *Designing Evaluations of Educational and Social Programs*. San Francisco: Jossey-Bass, 1987.

9. Fayers PM and Hand DJ. Generalization from phase III clinical trials: survival, quality of life, and health economics. Lancet 1997;350:1025-1027.

10. Hargreave F, Dolovich J et al. The assessment and treatment of asthma: A conference report. J Allergy Clin Immunol 1990;85:1098-1111.

11. Anonymous. International Consensus Report on the Diagnosis and Management of Asthma. Clin Exper Allergy 1992;22: Supp 1.

12. Kaliner, M. How the current understanding of the pathophysiology of asthma influences our approach to therapy. J Allergy Clin Immunol 1993;92:144-147.

13. Tarlo SM, Broder I et al. Six-month double-blind, controlled trial of high dose, concentrated beclomethasone dipropionate in the treatment of severe chronic asthma. Chest 1988;93: 998-1002.

14. Groot CA, Lammers JW, et al. Effect of inhaled beclomethasone and nedocromil sodium on bronchial hyperresponsiveness to histamine and distilled water. Eur Resp J 1992;5:1075-82.

15. Tinkelman DG, Reed CE et al. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children . Pediatrics 1993;92: 64-77.

16. Suissa S, Dennis R, Ernst P et al. Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma. Ann of Int Med 1997;126:177-183.

17. Ross RN, Morris M, Sakowitz SR et al. Cost-effectiveness of including cromolyn sodium in the treatment program for asthma: a retrospective, record-based study. Clin Ther 1988;10:188-203.

18. Campbell LM, Simpson RJ, Turbitt ML et al. A comparison of the cost-effectiveness of budesonide 400mcg/day and 800mcg/day in the management of mild-to-moderate asthma in general practice. BMJ 1993;6:67-74.

19. Connet GJ, Lenney W and McConchie SM. The cost effectiveness of budesonide in severe asthmatics aged one to three years. Br J of Med Econ 1993;6:127-134.

20. Sculpher MJ, Buxton MJ. The episode-free day as a composite measure of effectiveness. Pharmacoeconomics 1993;4:345-352.

21. Rutten-van Molken MPMH, van Doorslaer EKA, Jansen MCC et al. Cost-effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. Pharmacoeconomics 1993;4: 257-70.

22. Pererra BJC. Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country. Arch Dis Child 1994;72: 312-316.

23. Rutten-van Molken MP, Van Doorslaer EK, Jansen MC et al. (1995) Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. Am J Resp Crit Care Med 151:975-82.

24. Booth PC, Wells NEJ, Morrison AK. A comparison of the cost effectiveness of alternative prophylactic therapies in childhood asthma. Pharmacoeconomics 1996;10: 262-268.

25. Thomas K, Peter JV, Cherian AM et al. Cost-effectiveness of inhaled β-agonists v. oral salbutamol in asthma: a randomized double-blind cross-over study. Nat Med J India 1996;9:159-162.

26. Price DB, Appleby JL Fluticasone propioonate: an audit of outcomes and cost-effectiveness in primary care. Resp Med 1998;92:351-353.

27. Balkrishnan R, Norwood GJ, Anderson A. Outcomes and cost benefits associated with the introduction of inhaled corticosteroid therapy in a Medicaid population of asthmatic patients. Clin Ther 1998;20: 567-580.

28. Mayo PH, Richman J et al. Results of a program to reduce admissions for adult asthma. Ann Int Med 1990;112: 864-71.

29. Bolton, MB, Tilley BV et al. The cost and effectiveness of an education program for adults who have asthma. J Gen Internal Med 1991;6: 401-7.

30. Trautner C, Richter B, et al. Cost-effectiveness of a structured treatment and teaching programme on asthma. Eur Resp J 1993;6:1485-91.

31. Anonymous Integrated care for asthma: a clinical, social, and economic evaluation. Grampian Asthma Study of Integrated Care (GRASSIC). BMJ 1994;308:559-64.

32. Greineder DK, Loane KC, et al. Reduction in resource utilization by an asthma outreach program. Arch Ped Med 1995;149: 415-20.

33. Pauley TR, Magee MJ, et al. Pharmacist-managed, physician-directed asthma management program reduces emergency department visits. Ann Pharmacotherapy 1995;29: 5-9.

34. Osterhaus JT, Townsend RJ. Incorporating pharmacoeconomic research into clinical trials. In: Bootman JL, Townsend RJ and McGhan WF (eds) Principles of Pharmacoeconomics. 2nd edn. Cincinnati: Harvey Whitney Books Company, 1996: 196-211.

35. Williams JI, Young W. Inventory of Studies on the Accuracy of Canadian Health Administrative Databases. Toronto: Institute for Clinical Evaluative Sciences, Pub. No 96-03-TR, December, 1996.

36. Mawhinney, H., S. L. Spector, et al. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. Ann Allergy 1991;66: 294-9.

37. Rand, C. S., R. A. Wise, et al. Metered-dose inhaler adherence in a clinical trial [see comments]. Am Rev Resp Dis 1992;146:1559-64.

38. American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. Am Rev Resp Dis 1993;147:1056-1061.

39. Krahn MD, Berka C, Langlois P et al. Direct and indirect costs of asthma in Canada, 1990. Can Med Assoc J 1996; 154: 821-831.

40. Laurier C, Kennedy W, Gautrin D, Ghezzo H, Paré M, Labbé D, Contandriopoulos AP. Rate and cost of hospitalisations for asthma in Quebec: an analysis of 1988-1995 data. Submitted to Chronic Diseases in Canada (February, 1999).

The following tables and graphics provide information from supplemental analyses performed, the results of which were mentioned in the preceding article.

Appendices to Chapter 5

Table 5.5 Cross-tabulation of annual total cost categories: trial period, non-trial period

Trial period	Non-trial period	
	< $600 N (% column)	$600 + N (%column)
< $600	17 (46%)	3 (9%)
$600 +	20 (54%)	31 (91%)

Table 5.6 Cross-tabulation of annual ambulatory physician cost categories: trial period, non-trial period

Trial period	Non-trial period	
	< $100 N (%column)	$100 + N (%column)
< $100	24 (83%)	24 (57%)
$100 +	5 (17%)	18 (43%)

Table 5.7 Cross-tabulation of annual total cost except iCST categories: trial period, non-trial period

Trial period	Non-trial period	
	< $300 N (%column)	$300 + N (%column)
< $300	29 (76%)	19 (58%)
$300 +	9 (24%)	14 (42%)

Table 5.8 Cross-tabulation of annual anti-asthmatic cost categories: trial period, non-trial period

Trial period	Non-trial period	
	< $600 N (%column)	$600 + N (%column)
< $600	32 (59%)	1 (6%)
$600 +	22 (41%)	16 (94%)

Figure 5.3 Influence of inhaled corticosteroid dose on total costs, trial period, non-trial period

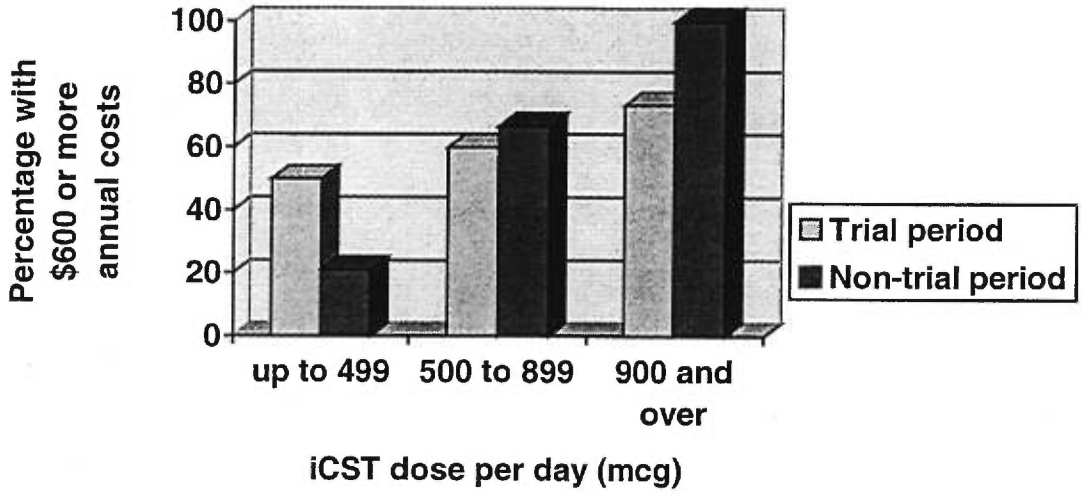


Figure 5.4 Influence of inhaled corticosteroid dose on all anti-asthmatic medication costs, trial period, non-trial period

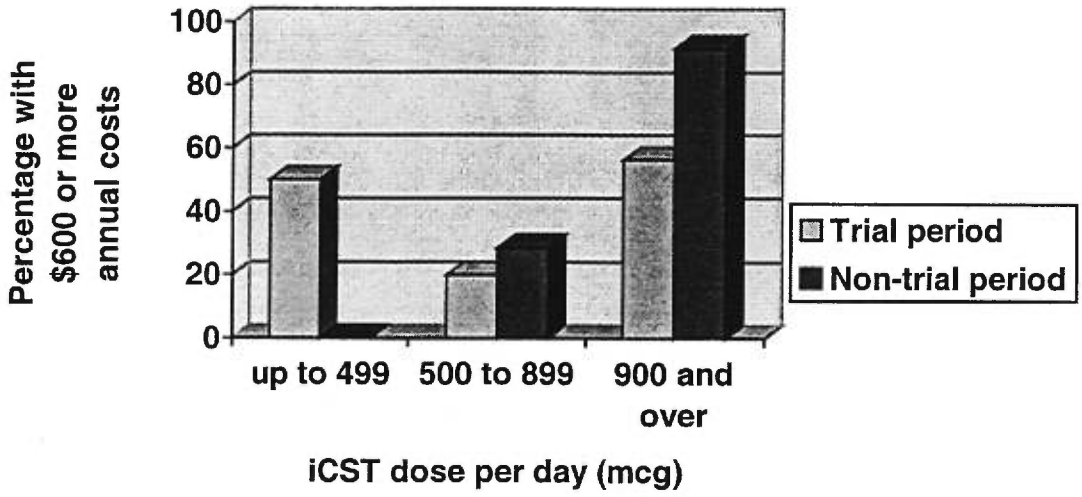
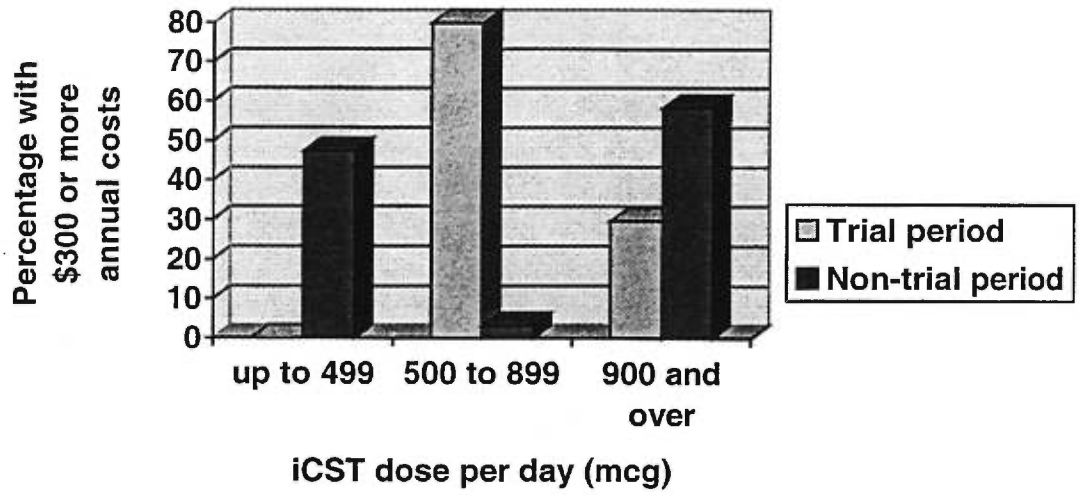


Figure 5.5 Influence of inhaled corticosteroid dose on non-iCST costs, trial period, non-trial period



Chapter 6

Cost-efficacy vs. cost-effectiveness: How does measurement in clinical trial subjects affect the ability to generalise use and cost of health services to 'real life' subjects?

The following article is being submitted for publication to *PharmacoEconomics.*

Cost-efficacy vs. cost-effectiveness: How does measurement in clinical trial subjects affect the ability to generalise use and cost of health services to 'real life' subjects?

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ABSTRACT

To explore the impact of having been recruited as a subject for a controlled clinical trial on the use and cost of asthma-related health services, these services were estimated for a group of subjects who had participated in clinical trials for asthma therapy and had taken inhaled corticosteroids (iCSTs), and compared to those services used by a similar group of subjects who had never participated in a trial. Two samples of asthmatic subjects who had taken iCSTs were recruited and those for whom all resource use

information was available constituted the samples for analysis: those who had participated in clinical trials (TS, n=46) and those who had not (NS, n=51). Their average use and cost of anti-asthma medications, ambulatory physician services, asthma hospitalisations and emergency room services were collected for a period not exceeding 6 months and compared. The relationship of age group, gender, asthma severity, year of data collection period and geographic location (Montreal or Quebec City) to these outcome variables was explored. In a logistic regression analysis controlling for age group, asthma severity, year of data collection and geographic location, TS were more likely to use higher (400µg or more) daily doses of inhaled corticosteroids than NS (Odds Ratio [OR] 3.3, 85% Confidence Interval [CI] 1.5 – 7.3). TS were less likely to visit the emergency department than were NS (OR 0.3, 85%CI 0.1 – 0.6), and less likely to have 2 or more general practitioner visits per year (OR 0.3, 85%CI 0.2 – 0.6). Log transformed total asthma related costs did not differ in TS and NS. This study shows that certain categories (including iCSTs, emergency department physician services, and general practitioner physician services) differed in two groups of subjects (having or not having been enrolled in a clinical trial) taking iCSTs for their asthma, but we could not conclude that there was a difference in the total cost of asthma-related health services.

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Montreal. Dr. Laurier holds the Hoechst Marion Roussel chair on Use of Medications: Policy and Outcomes at the University of Montreal.

INTRODUCTION

The randomised clinical trial (RCT) is the source of most of the data for the effect and the cost of treatments in health care. Thus it is the average effect of those treatments on the subjects which have been recruited for those trials which constitute the estimated effect and the cost of the use of the health care services for the purposes of cost-effectiveness estimates. The strength of the RCT is its internal validity, but the external validity is less laudable (1-3). The problem of how to generalise the results of the RCT to other situations is particularly difficult when the economic impact of the intervention is under scrutiny (4,5). Because that economic impact is used most often for the purposes of planning and budgeting over the long-term in heterogeneous populations in real life conditions, the limitations of the RCT are felt most acutely: the RCT uses a carefully screened group of subjects with homogenous characteristics under relatively artificial and controlled conditions.

The authors wished to examine the influence of having been selected for and having participated in a clinical trial on the use of health services to explore some of the aspects of the external validity issue. "External validity is simply the construct validity of the results of the study sample (utoS) generalised to

the study population (UTOS), which is then generalised to other populations (*UTOS). 'External' construct validity also concerns whether the sample of units (u), treatments (t), observations (o), and Setting (S) accurately match or represent the population of Units (U), Treatments (T), Observations (O), and Setting (S), and other populations of *U, *T, *O, and *S." (6) The difference examined by this study is an aspect of the unit, or subject, construct. The problems of demographic differences between the subject construct (age, gender, comorbidities and the like) have been discussed elsewhere (1-5), but there has been little examination of the impact of having been selected to participate in trial. It is this factor on which we wish to focus, exploring that difference while controlling for those demographic factors.

The example of the treatment of asthma by inhaled corticosteroids (iCSTs) was chosen as a pilot study. ICST therapy is an important part of the treatment of asthma and has been the subject of many clinical trials. In these trials, the subjects chosen for participation have been pre-screened for certain characteristics.

The main indicator of the differences is the use of asthma-related health services. The optimal use of iCSTs should result in the minimum utilisation of alternative treatments for the disease including beta-2 agonists (7), and visits to physicians, emergency departments and hospitals. Health services such

as these have been included as study end-points in economic evaluations of asthma medications (8-20).

For these reasons, the real life conditions use of asthma-related health services in a group of mild to severe asthmatic subjects using inhaled corticosteroids, who had been enrolled in clinical trials, were compared to that of a group of mild to severe asthmatic subjects also using inhaled corticosteroids, but who had never participated in a drug trial. This study estimated the differences in asthma related health services between these two populations and investigated how having been selected a trial subject influences the overall costs of asthma treatment. It is surmised that the RCT influenced the subject of the trial, and their use and cost of health services will be affected in part because of what they have learned from the trial situation.

METHODS

Sample Selection.

There were two samples drawn. For the TS, companies marketing inhaled corticosteroids and 3 hospital-based clinical trial research groups identified clinical trial studies involving adult asthmatic patients taking iCSTs, which were completed in Quebec between January 1, 1990 and March of 1997, and lasted 8 weeks or longer. The subjects who had taken an iCST during these trials were identified, and their consent to participate and allow release of their pharmacy records was sought.

For the Normal Setting Sample (NS), 6 pharmacies in the city of Montreal and 7 in Quebec City were asked to recruit asthmatic subjects, selecting for age group and period of medication use comparable to the TS. Because a physician diagnosis was not available in the pharmacy, inclusion criteria were 1) subject-reported physician diagnosis of asthma, 2) pharmacy-record use of inhaled corticosteroids, and 3) subject-reported history of relatively stable asthma for the preceding 4 years. Excluded from recruitment were individuals who had participated in any drug-related clinical trial, and those individuals with characteristics corresponding to major clinical trial exclusions. These were individuals reporting physician diagnosis of emphysema, those with pharmacy-record use of 4 or more short-term courses of oral steroid treatment in a 12 month period in that pharmacy, and, if over 45 years of age, a smoking history exceeding 20 pack-years (average number of packs per day X number of years smoking).

Data Collection.

To estimate the use of asthma-related health services under conditions of normal use, the TS subjects' use of health services was collected for a maximum period of 6 months immediately following the clinical trial which qualified them as candidate subjects for this study. The NS subjects' use of health services was collected for a two year period, and a window not exceeding 6 months was created in the same time-frame as the TS subjects'

period of health services use. A minimum period was established because the data collection end date was December 31, 1996, and a few of the windows were shortened because the end of the 6 month period fell after this date. The beginning of the data collection period (for medication use only) could be shorted if the oldest prescription in the pharmacy records fell after the beginning of the defined period of 6 months.

All defined health services were collected for the two groups during the periods established. Use of health services consisted of 1) the anti-asthma prescription medications dispensed to the subject by their community pharmacies, 2) consultation with family practitioners, respirologists or internal medicine specialists, 3) emergency department visits and 4) hospitalisations with a recorded diagnosis of asthma.

Prescription drug services were collected from all of the individual pharmacies identified by the recruited subjects. The subjects had been asked to provide the names and addresses of all pharmacies from which they purchased anti-asthma medications. Details of prescriptions dispensed for inhaled corticosteroids, bronchodilators, theophyllines, oral corticosteroids, and antibiotics were collected, and use or non-use of other major classes of medications during the study period were noted.

The presence of major comorbidities was estimated from the medications in the pharmacy records. The pharmacists noted the medications prescribed for the subject in any of several categories.[1] Asthma severity was estimated on the basis of the prescribed dose of anti-asthma medications[2] as contained in the pharmacy records. If more than one prescribed dosage was in the file the most recently listed during the data collection period was used. Those prescribed 1000µg or more per day of inhaled corticosteroid equivalent to beclomethasone were deemed severe, and those prescribed lower were deemed mild to moderate. [3] None of the subjects were classed very severe, as uncontrolled or very severe asthma were exclusion criteria for the study.

Physician consultation information was obtained from the data banks of the government-funded provincial health insurance (RAMQ), and hospitalisation information from the provincial ministry of health. Physician visits were not restricted to any particular diagnosis, as the validity of the diagnosis in this type of data base has not been ascertained for the specific services[4] delivered. (22,23)

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[1] Major comorbidity was coded for use of medication in one or more of the following categories: antineoplasics, antiparkinsonians, cardiovascular medications, antihypertensives, anticonvulsants, antidepressants, antidiabetics or insulin, cyclosporin.

[2] The dose of anti-asthma medications required to control the patient's asthma forms part of the tri-part score recommended (21) for use in determining the degree of disability of the disease, and is the only element available for the subjects recruited.

[3] Occasionally, the prescribed dosage is missing or the file indicates 'Take as directed' or some similar wording.

[4] We would not be using the diagnosis here to determine whether the subject has a particular health problem or not (diagnoses in these types of data banks have been used to identify subjects with a particular problem), but to determine if the service had been delivered for that health problem. The visit to the physician could have been for the subject's asthma, or other

Costs for drug use were calculated by multiplying the prescription medications dispensed as recorded in the pharmacy files by prices based on the 1996 list of medications covered by the public plan, together with 6.5% wholesale upcharge, and a pharmacy service fee of $7.77 per prescription dispensed[5]. Hospitalisation costs were based on the 1996 per diem hospital stay cost (517$Can) for Sacré-Cœur Hospital. The cost of physician visits were based on provincial reimbursement levels for 1996. Emergency services use consisted of hospital emergency department based physician visits and the 1995 per-episode cost of $128 for Sacré-Cœur Hospital. Total asthma-related costs were the sum of the above.

Data Analyses.

Quantities dispensed of inhaled corticosteroids and short-term bronchodilators were calculated on a daily basis, by dividing the total quantity dispensed during the measured period by the number of days in that period. All quantities dispensed during the study period were included: we did not search back before the beginning of the study period to look for outstanding prescriptions, nor did we attempt to allocate quantities of prescriptions received near the end of the period. All other quantities and cost of services were estimated on an annual basis, by dividing the quantity or the cost during

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health problems which were not related to asthma. Without a chart review, it is difficult to determine the association of the diagnosis with the service.

[5] The service fee is the average dispensing fee reported for 1966 by the Quebec pharmacy owners association (AQPP).

the measured period by the number of days during that period, then multiplying the daily average by 365.

The continuous variables were first tested for normal distribution. Non-normally distributed variables were either transformed into base 10 Log, or if there was two-modal distribution, they were reclassified as categorial variables. The influence of group (TS vs. NS) and the independent variables of age group, gender, location, and year of data (1995 or 1996; 1990 through 1994) was tested on the log transformed outcome variables by way of simple linear regression analysis, and on the outcome categories by way of logistic regression analysis. Those found to be significant ($p<0.15$) were then entered with the group variable in multiple regression analyses to estimate the adjusted results.

The analysis of the data was done with SPSS for Windows version 7.5.1. Because the observation of tendencies and directions of changes in use were the main outcomes of interest, an α of 0.15 was used as the threshold for significance.

RESULTS

Samples.

For the TS 154 subjects were recruited in two cities, Montreal and Quebec City. For the NS a total of 52 subjects were recruited. The recruitment process is detailed in a footnote using 2 of the 13 recruiting pharmacies, 1 each in of Quebec City and in Montreal. Of an initial listing of 266 users of inhaled corticosteroids in the 2 pharmacies, the pharmacist screened for recent attendance, appropriate age group, time period, and probable indication of asthma from the drug use profile, yielding a resulting 25% (67) to be contacted. Of these, only 58% (39) were able to be contacted by telephone or in person, and of these 26% (10 persons) were found to be eligible for the study. The balance had either smoked more than 20 pack-years (11), been involved in a trial (7), said they did not have asthma (8), or had recently increased crises (2). Therefore, of the initial 266 pharmacy patients, only 6 of the 10 contacted eligible subjects were recruited; 1 refused, and 3 did not return their signed consent forms.

Data.

Information on physician services and hospitalisations were obtained for all but one (TS) subject. Information on ambulatory pharmacy services was obtained for 75 of the TS subjects and all NS subjects, except that for one subject in the NS, the data for ambulatory drug use was unavailable for any part of the data collection period required. Although all subjects identified their pharmacies, many pharmacies keep records for no longer than 2 years. The periodic purging of electronic patient records in pharmacies meant that for half of the subjects in the TS no pharmacy services information was available. For 29 of the 75 TS subjects, the resources use information period fell prior to the trial, so the analysis was conducted using on those 46 subjects in whom non-trial period measurement fell after the trial period. Table 1 contains the description of the subjects for which all health services information was available.

The actual data collection period for use of medications and pharmacy services was an average of almost 6 months,[6] the period for use of other health services was also for an average period just under 6 months, with a minimum of 3.9 months.

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[6] In one subject the period was only 7 weeks, the next shortest period was almost 3 months. The average was 176 days.

Table 1 Description of recruited subjects

	TRIAL SAMPLE N=46		NORMAL SETTING SAMPLE N=51	
	n	%	n	%
Gender				
Male	18	39.1	8	15.7
Female	28	60.9	43	84.3
Age group				
20 to 44	17	37.0	22	43.1
45 to 59	16	34.8	7	13.7
60 to 79	13	28.3	22	43.1
Asthma severity*				
Mild/moderate	12	26.1	19	37.3
Severe	28	60.9	28	54.9
Unknown	6	13.0	4	7.8
*Comorbidities (major)***				
None	37	80.4	31	60.8
One or more	9	19.6	20	39.2
Location†				
Montreal	28	60.9	30	58.8
Quebec	18	39.1	21	41.2
Overall	46	100	51	100

* Calculated from prescribed dosage of anti-asthma medications. Those with 1000µg per day or more were assumed to be severe, the others were assumed to be mild to moderate.

** Major comorbidity was coded for use of medication according to the pharmacy records in one or more of the following categories: antineoplasics, antiparkinsonians, cardiotropes, antihypertensives, anticonvulsants, antidepressants, antidiabetics or insulin, cyclosporin.

There are differences between the two groups. A subject in the NS is more likely to be female ($p<0.01$),[7] older ($p=0.04$), have less severe asthma ($p=0.09$), and have one or more severe comorbidities ($p=0.04$). Although not significant, a higher proportion of the TS was found to have more severe asthma ($p=0.31$). We can surmise that it was easier to recruit women who met the inclusion criteria in the NS, because we required a certain (although not

[7] Pearson chi-square.

strict) non-smoking history, and there appears to have been few men having met this criteria in the NS population. The difference in severity and comorbidity is likely to be the result of the selection process for the clinical trial: the subjects of the trial have been chosen for their lack of concurrent disease, and more severe asthmatics may have been referred to specialists for treatment by their general practitioners.

Medications: proportion of users, quantity and cost.

Before adjustment for potential confounders, there was no significant difference between the proportion of users of one or more prescriptions of short-term bronchodilators: TS 58.7% vs. NS 60.8% (Odds Ratio [OR]=0.9 85% Confidence Interval [CI] 0.5 to 1.7), iCSTs: 65.2% vs. 54.9% (OR=1.5, 85% CI 0.8 to 2.8), oral corticosteroids: 13.0% vs. 13.7% (OR=0.9, 85% CI 0.4 to 2.2), theophyllines: 0% vs. 15.7%, (OR<0.01, 85% CI <0.01 to >100), antibiotics: 21.7% vs. 31.4% (OR=0.6 85% CI 0.3 to 1.2), long-acting bronchodilators: TS 13.0% vs. 5.9% (OR=2.4 85% CI 0.8 to 7.0), nor any anti-asthmatic: 84.8% vs. 80.4% (OR=1.4 85% CI 0.6 to 3.0). There was still no significant difference in these variables after adjusting for differences in control variables (age group, gender, year of data, severity, city, comorbidity).

The TS used an average of 517µg (SD=572) per day of iCSTs, higher (p=0.04)[8] than the NS at 327µg (SD=535). There was little difference seen

[8] Mann-Whitney

between the two groups in the average daily quantities used of short-acting bronchodilators (TS 2.0 [SD=2.4] puffs per day (NS 2.7 [SD=2.5] puffs per day, p=0.61).

The average daily quantity of iCSTs was divided into two categories (based on a figure close to the mean): low or none (less than 400mcg per day), or moderate to high (400mcg per day or more). The TS was 3.8 times more likely to use the higher average daily dose than the NS, controlling for severity of asthma, year of data and city. (Table 2)

The TS showed a higher average annual cost of iCSTs, $291 (SD=324), than the NS cost of $182 (SD=301) (p=0.04) [9], and a higher average annual cost of all anti-asthmatic medications: $468 (SD=454) vs. $350 (SD=449) (p=0.07). There was no difference seen between the two groups for average annual cost of anti-asthma medications other than iCSTs (p=0.9): $177 (SD=254) vs. $168 (SD=449).

Annualised costs of iCSTs were divided into two categories, low or none (less than $150), or high ($150 or more); as were anti-asthma medications other than iCSTs, low or none (less than $100), or high ($100 or more); and all anti-asthma medications, low or none (less than $250), or high ($250 or more). These divisions were based roughly on their respective median values, and

[9] Mann-Whitney

resulted in a fairly even distribution of the cases. The results of the comparisons between the two groups by logistic regression are found in Table 2.

Table 2 Anti-asthma medication use, Trial Sample and Normal Setting Sample: log linear regressions on average quantities and costs

Log linear regression	Crude Regression of Group*	Adjusted Regression of Group
Average daily quantity (µg) of:	*(OR, 85% CI)*	*(OR, 85% CI)*
iCSTs (<400 vs. >=400)	3.3 (1.7 – 6.4)	3.8 (1.7 –8.7) †
Average annual cost ($CAN) of:		
ICSTs (<150 vs. >=150)	3.1 (1.7 – 5.8)	3.3 (1.5 – 7.3) §
Other anti-asthma med (<100 vs. >=100)	0.8 (0.4 – 1.3)	--
Any anti-asthma med (<250 vs. >=250)	2.0 (1.1– 3.7)	1.8 (0.9–3.6) §§

* Group (Trial=1, Normal Setting=0)
** iCSTs=inhaled corticosteroids
† Adjusted for severity of asthma, year of data, and city.
§ Adjusted for severity of asthma.
§§ Adjusted for year of data and severity of asthma.

Physician services: proportion of users, quantity and cost.

Before adjustment, there was little difference between the proportion of individuals with one or more physician visits: TS 93.5% vs. NS 86.3% (OR=2.3 85% CI 0.8 to 6.5), with one or more visits in the hospital setting: 4.3% vs. 7.8% (OR=0.5 85% CI 0.2 to 1.9), or in the ambulatory setting: 89.1% vs. 86.3% (OR=1.3 85% CI 0.5 to 3.2). There was still no significant difference in these variables after adjusting for control variables.

Before adjustment, individuals in the TS were less likely to have one or more visits with a general practitioner (69.6%) than those in the NS (86.3%) (OR 0.4, 85% CI 0.2 to 0.8), but the difference disappeared when adjusting for age group and city (OR=0.5 85% CI 0.2 to 1.0). They were more likely to have one or more visits with a specialist, both by crude analysis (OR=11.8 85% CI 5.7 to 24.6) and after controlling for age group and city (OR=13.5 85% CI 5.9 to 30.8). They were also less likely to have one or more visits in the emergency department setting, both by crude analysis (OR=0.2 85% CI 0.1 to 0.5) and adjusting for age group (OR=0.3 85% CI 0.1 to 0.6).

Table 3 Physician visits, Trial Sample and Normal Setting Sample: log linear regressions on average quantities and costs

Log linear regression	Crude Regression of Group*	Adjusted Regression of Group
Average annual number of:	*(OR, 85% CI)*	*(OR, 85% CI)*
General practitioner (<4 vs. >=4)	0.2 (0.1 – 0.5)	0.3 (0.2 – 0.6)**
Specialist (0 vs. >=1)	11.8 (5.7 – 24.6)	12.0 (4.9 – 29.0) †
Total ambulatory (<4 vs. >=4)	0.6 (0.3 – 1.1)	----
Average annual cost ($CAN) of:		
General practitioner (<85 vs. >=85)	0.2 (0.1 – 0.4)	0.3 (0.1 – 0.5) ††
Specialist (0 vs. >=1)	11.8 (5.7 – 24.6)	12.0 (4.9 – 29.0) †
Total ambulatory (<120 vs. >=120)	0.9 (0.5 – 1.6)	----

* Group (Trial=1, Normal Setting=0)
** Adjusted for age group and year of data.
† Adjusted for age group, severity of asthma and city.
†† Adjusted for age group.

Again using the median of the variable, the number and cost of physician visits were regrouped into 2 categories.[10] The number of general practitioner visits and the number of ambulatory physician visits were both regrouped as either low (less than 4) or higher (4 or more); the number of specialists was regrouped as none or one or more. The cost of general practitioner visits was regrouped as low (less than $85) or higher ($85 or more), and the cost of ambulatory visits was regrouped as low (less than $120) or higher ($120 or more). There was no other practical regrouping of cost of specialist visits than none or more than none, so the analyses were identical to that of the number of specialist visits.

Before adjustment the TS showed a higher average annual number of specialist physician visits: 1.90 (SD=1.85) vs. 1.66 (SD=8.65) ($p<0.01$)[11] and a lower average annual number of general practitioner visits: 5.08 (SD=10.69) vs. 8.62 (SD=7.67) ($p<0.01$). There was no significant difference seen between the two groups for average annual number of ambulatory physician visits: TS 5.73 (SD=6.83) vs. NS 7.11 (SD=6.50) ($p=0.29$). Results of the regression analyses comparing the two groups are found in Table 3.

Similar results are seen when the number of visits are measured in cost terms. Before adjustment the TS showed a higher average annual cost of

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[10] The median value for number and cost of specialist visits was 0. Using the regrouping, there were 60 cases in the 0 category, leaving 37 in the other. Any other regrouping would have increased the number of cases in the 'lower" category.

[11] Mann-Whitney

specialist physician visits: $62 (SD=64) vs. $47(SD=214) ($p<0.01$) [12], and a lower average annual cost of general practitioner visits: $120 (SD=266) vs. $196 (SD=185) ($p<0.01$). There was no significant difference seen between the two groups for average annual cost of ambulatory physician visits: $157 (SD=196) vs. $174 (SD=166) ($p=0.73$). Result of the logistic regression analyses are found in Table 3.

Hospitalisations.

The proportion of those hospitalised for one or more days with a principal diagnosis of asthma was very low: there were no hospitalisations in the NS and only one in the TS.

Regression of variables on Overall Costs.

Estimated total annual asthma-related health services costs were $696 (SD=583) for the TS and $688 (SD=629) for the NS. Overall costs were non-normally distributed (skewness=1.3). To normalise the data, a sum of $100 was added to total annual costs, then the sum was transformed to base 10 log (skewness=-0.13). The simple linear regression comparing group (TS vs. NS) was non-significant ($p=0.63$). In a multiple regression of group together with

[12] Mann-Whitney

those variables significant by simple regression, group stayed non-significant (p=0.72). The resulting model[13] is as follows:

$$Y = 4.39 + 0.02\ Group + 0.19\ Age + 0.26\ Severity + 0.20\ Year + e$$

Where Y: Base 10 log of (Annualised total anti-asthma costs + $100)

Group: 1=Trial; 0=Normal Setting

Age: 1= Age 60 or more in 1996; 0=Age under 60 in 1996

Severity: 1=severe; 0=mild, moderate

Year: 1=1995 or 1996; 0=1990 to 1994

e: error term

DISCUSSION

In this study, we did not see that the estimated cost of total asthma-related health services in individuals with mild to severe disease and taking inhaled corticosteroids for their asthma, who had never been the subject of a clinical trial, were different from those who had participated. Higher total anti-asthma costs were associated with increased age, more severe disease, and more recent treatment period. There were, however, some interesting differences between the two groups seen in certain categories of health services use and cost, most notably in the use and cost of inhaled corticosteroids, and the

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[13] The adjusted R-squared of the model is 0.22

number and cost of general practitioner and specialist visits. Indeed, in regression analyses, it was estimated that trial participants were likely to use higher doses of inhaled steroids and at a higher annual cost. Additionally, they were more likely to see a specialist, and to have fewer visits to general practitioners at a lower annual cost than were individuals who had never so participated.

The information on the use of health services was gathered in the same way for both groups. There may be some services unreported, specifically medication use, but there is no reason to believe that there will be a systematic difference between the two groups. The same can be said for physician services which are not fee-for-service. A certain portion (14%) of physicians in Quebec are reimbursed by salary or vacation pay (24), but this represents a minor percentage of overall physician services.[14] Additionally, not all the eligible subjects were recruited, more for reasons of inability to trace the individuals than for active refusal. Again, there is no reason to believe that a systematic difference would be seen between the recruited and non-recruited groups.

The purpose of the study led to the method of recruiting the two samples. We wanted to select individuals who had not been chosen nor necessarily had even been candidates for clinical trials for our NS. We did, however, attempt

[14] This does not include salaries for residents or fees for laboratory medicine services.

to create inclusion and exclusion criteria for the NS which would eliminate those not eligible for the clinical trials from which the Trial subjects were drawn, and approximate the severity and stability of the disease in the TS. The individuals were screened by self report questions as to diagnosis, smoking history and stability of their asthma (both severity and frequency of crises). In addition, they were screened by their pharmacists with respect to the receipt of inhaled corticosteroids and prescription of high doses of oral steroids indicative of asthma crises. We were looking for the influence of the trial on the subjects, not the differences in disease state.

The difficulty we had in finding eligible subjects is indicative of the stringency of the criteria. The number of individuals who were ineligible due to previous participation in a clinical trial is particularly revealing – the 'creaming' of the healthier segment for the trial population is not a fantasy in this disease group. It should also be noted that there was a particularly high proportion of individuals over the age of 45 approached for the NS who had smoked for longer than 20 years.

We used a p-value of 0.15 as the level of significance for the differences in use and cost of health services, rather than the more commonly accepted rate of 0.05. We feel this level is reasonable in this exploratory study, as we were looking more for the direction of differences and an indication of what would be important to explore further. The consequences of a type I error are also

financial ones, as opposed to the health consequences for clinical alternatives. The main question is whether the decision-maker requires a high precision for such economic data, or if the risk of inferential error of this degree would be acceptable. (25) The results using a relaxed threshold nonetheless allow us to meet the objectives of the study: to see in what manner and in what direction the groups differ in their use and cost of (most) of the health services.

The sample sizes are small, however, for studies on total cost of health services. Costs in health care tend to be highly variable, particularly when dealing with costs such as hospital and emergency visits with a relatively low population occurrence and a high unit value. Real differences between the two populations may not have been seen because of this limitation. There were 87 subjects with complete information on resources use and for whom we were able to code severity, 40 in the TS and 47 in the NS. The huge variation in the total costs, particularly in the NS is responsible for our inability to show any difference between the two groups. Even with the p-value of 0.15 and using a β of 0.3, the difference seen between the two groups would only have been significant if the overall standard deviation was $275 or less, however the observed SD was over $600.

Severity of disease has been measured by a proxy: the prescribed dose of anti-asthma medications. This leads to a possible confounding by different

compliance patterns in the two groups. A treating physician may tend to increase the dose of his patient's medications thinking the asthma uncontrolled at lower dose, when in reality the lack of control is due to non-optimal compliance with the therapy. There is substantial evidence that even clinical trial subjects have poor compliance with their medication regimens, (26-28) and subjects in the normal setting are likely to be even less rigorous.

We chose to analyse only a portion of the TS subjects, those whose use and cost of services were measured after their enrolment in the relevant RCT. All the same analyses were conducted including those subjects in which the use was measured before their enrolment, and the results were almost identical, with the exception of some changes in significance. We normally would expect some change in the effect of learning from the RCT including these subjects. However, according to the clinical investigators of the original trials, most of the subjects recruited in the trials had been enrolled in previous trials, so we did not have a group of 'naïve' trial subjects. This should mean that any improved compliance behaviours learned from having participated in an RCT would be present in the majority of the group.

Finally, our populations are different, and there is a likelihood that the TS is likely more ill with their asthma than the NS, and the proxy index we used to control for this severity is insufficient to account for that difference. A study

has shown that specialists' (in that case allergists) patients had more severe asthma than the patients of general practitioners (29). In the community, asthmatics with great difficulties with their disease would have already been referred by their family practitioners to a specialist. Therefore the population from which the NS can be recruited would have relatively less severe disease. The TS subjects had higher costs of iCST than did the NS subjects, but this was not sufficient to cause a significant difference in total costs, and we could therefore suppose that the TS are better controlled. The NS can be less intensely treated, but this does not reflect on their overall cost of services, because they were not so severe.

Additionally, there could be other 'hidden' differences which would not be normally controlled for in epidemiological studies. There could be a selection bias in the TS group. We could postulate that patients are more likely to be referred to specialists if they are better able to express themselves and describe their symptoms and their difficulties. Certainly the specialists are likely to select their patients for trials who are more likely to be able to meet the run-in period requirements, and these individuals are likely to be the more compliant.

CONCLUSION

Even when controlling for measured differences in demographics, the use and cost of certain types of asthma-related health services (iCSTs, general

practitioner and specialist physician visits) differed between the subject of a clinical trial and a subject who had never participated in a trial. We speculate this difference is accounted for by having been so selected and having learned something from trial participation.

Our study could detect no difference in overall cost of asthma-related health services in individuals taking inhaled corticosteroids for their asthma, whether or not they had been enrolled in a clinical trial, but there was a large difference in the variance of the cost of these services between the two groups. However, use of certain categories (including iCSTs, emergency department physician services, and general practitioner physician services) differed. Interpreting to real life from trial situations, we should generally expect to see a larger variance in the use and cost of health services, a greater use in real life of the services of general practitioners, and a lower use of specialists, and a lower use of inhaled corticosteroids.

The use and cost of health services is a result of the iCST treatment, a number of subject construct factors which differentiate the subjects of the RCT from individuals who have never been chosen, and the interaction of the treatment with these subject construct factors. We could speculate the difference would partially be due to the learning experience of the trial. Trial subjects may also be more educated (they have to be able to follow rigid and sometimes complex treatment schedules and properly complete symptom and

drug use diaries). These factors are difficult to separate from the iCST treatment itself and they may additionally interact with the iCST treatment to affect use and cost of health services.

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REFERENCES

1. Feinstein, A. R. (1988) Problems, pitfalls, and opportunities in long-term randomised trials. Drug Research and Drug Development in the 21st Century, Bayer, AG Centenary Symposium.

2. Susser, M. (19950 Editorial: The tribulations of trials--intervention in communities. *Am J Public Health* **85**, 156-158.

3. Cunningham, W.E., Bozzette, W. A,, Hays, R. D., Kanouse, D. E. and Shapiro, M. F. (1995) Comparison of health-related quality of life in clinical trial and nonclinical trial human immunodeficiency virus-infected cohorts. *Medical Care* **33**, AS15-AS25.

4. Rittenhouse, B. E. and O'Brien B. J. (1996) Threats to the validity of pharmacoeconomic analyses based on clinical trial data. Ch. 26 of Spilker, B. (ed) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven.

5. Fayers, P. M. and Hand, D. J. (1997) Generalization from phase III clinical trials: survival, quality of life, and health economics. *Lancet* **350**, 1025-1027.

6. Conrad, K. J. and Conrad, K. M. (1994) Reassessing validity threats in experiments. Focus on construct validity. *New Directions for Program Evaluation* **63**, 5-25.

7. Kaliner, M. (1993) How the current understanding of the pathophysiology of asthma influences our approach to therapy. *J Allergy Clin Immunol* **92**, 144-147.

8. Ross, R. N., Morris, M., Sakowitz, S.R. and Berman, B. A. (1988) Cost-effectiveness of including cromolyn sodium in the treatment program for asthma: a retrospective, record-based study. *Clin Ther* **10**, 188-203.

9. Campbell, L. M., Simpson, R. J., Turbitt, M. L. and Richardson, P.D.I. (1993) A comparison of the cost-effectiveness of budesonide 400mcg/day and 800mcg/day in the management of mild-to-moderate asthma in general practice. *BMJ* **6**, 67-74.

10. Connet. G. J., Lenney, W. and McConchie, S.M. (1993) The cost effectiveness of budesonide in severe asthmatics aged one to three years. *Br J of Med Econ* **6**, 127-134.

11. Sculpher, M. J. and Buxton, M. J. (1993) The episode-free day as a composite measure of effectiveness. *Pharmacoeconomics* **4**, 345-352.

12. Rutten-van Molken, M. P. M. H., van Doorslaer, E. K. A., Jansen, M. C. C., Van Essen-Zandvliet, E. E. and Rutten, F. F. H. (1993) Cost-effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. *Pharmacoeconomics* **4**, 257-70.

13. Pererra, B. J. C. (1994) Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country. *Arch Dis Childhood* **72**, 312-316.

14. Rutten-van Molken, M. P., Van Doorslaer, E. K., Jansen, M. C., Kerstjens, H. A. and Rutten, F. F. (1995) Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* **151**, 975-82.

15. Booth, P. C., Wells, N. E. J. and Morrison, A. K. (1996) A comparison of the cost effectiveness of alternative prophylactic therapies in childhood asthma. *Pharmacoeconomics* **10**, 262-268.

16. Thomas, K,, Peter, J. V., Cherian, A. M. and Guyatt, G. (1996) Cost-effectiveness of inhaled β-agonists vs oral salbutamol in asthma: a randomised double-blind cross-over study. *Nat Med J of India* **9**, 159-162.

17. Price, D. B. and Appleby, J. L. (1998) Fluticasone proprionate: an audit of outcomes and cost-effectiveness in primary care. *Resp Med* **92**, 351-353.

18. Balkrishnan, R., Norwood, G. J. and Anderson, A. (1998) Outcomes and cost benefits associated with the introduction of inhaled corticosteroid therapy in a Medicaid population of asthmatic patients. *Clin Ther* **20**, 567-580

19. Pearson, M. G. and Johnson, F. N. (1998) Pharmacoeconomic aspects of fluticasone propionate in the treatment of asthma. *Rev Cont Pharm* **9**, 591-599.

20. Steinmetz, K. O., Volmer, T., Trautmann, M. and Kielhorn, A. (1998) Cost effectiveness of fluticasone and budesonide in patients with moderate asthma. *Clin Drug Inv* **16**, 117-123.

21. American Thoracic Society. (1993) Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Resp Dis* **147**, 1056-1061.

22. Osterhaus, J. T. and Townsend, R. J. (1996) Incorporating pharmacoeconomic research into clinical trials. In: Bootman, J. L., Townsend, R. J. and McGhan, W. F. (eds) *Principles of Pharmacoeconomics*. 2nd edn. Cincinnati: Harvey Whitney Books Company, 196-211.

23. Pauley, T. R., Magee, M. J. and Cury, J. D. (1995) Pharmacist-managed, physician-directed asthma management program reduces emergency department visits. *Ann Pharmacotherapy* **29**, 5-9.

24. Régie de l'assurance-maladie du Québec. (1997) *Statistiques Annuelles 1996* Quebec: Minister of Health and Social Services.

25. Drummond, M. F., O'Brien, B., Stoddart, G. L. and Torrance, G. W. (1998) *Methods for the Economic Evaluation of Health Care Programmes.* 2nd edn. Oxford: Oxford University Press, p. 238.

26. Mawhinney, H., Spector, S. L., Kinsman, R. A., Siegel, S. C., Rachelefsky, G. S., Katz, R. M. and Rohr, A. S. (1991) Compliance in clinical trials of two nonbronchodilator, antiasthma medications. *Ann Allergy* **66**, 294-299.

27. Rand, C. S., Wise, R. A., Nides, M., Simmons, M. S., Bleecker, E. R., Kusek, J. W., Li, V. C. and Tashkin, D. P. (1992) Metered-dose inhaler adherence in a clinical trial. *Am Rev Resp Dis* **146**, 1559-1564.

28. Schmier, J. K. and Leddy, N. K. (1998) The complexity of treatment adherence in adults with asthma: challenges and opportunities. *J Asthma* **35**, 455-472.

29. Vollmer, W. M., O'Hollaren, M., Ettinger, K. M., Stibolt, T., Wilkins, J., Buist, S., Linton, K. L. P. and Osborne, M. L. (1997) Speciality differences in the management of asthma a cross-sectional assessment of allergists' patients and generalists' patients in a large HMO. *Arch Intern Med* **157**, 1201-1208.

Chapter 7

Generalising from the clinical trial to the normal setting

This chapter puts together the overall comparison of measurement of cost which had been separately analysed in Chapters 5 and 6, and compares the costs of asthma-related health services which was estimated using the subject and treatment construct of the RCT, with the estimated measurement of those costs in real life.

There are two cost variables compared, the total estimated annual costs of asthma-related health services, and those total costs net of iCSTs. This chapter looks at the question of whether the cost part of these cost-efficacy measures can be generalised to normal, real-life conditions – whether they can be used as a reasonable estimate for a cost-effectiveness measure (the real life cost to effect measure).

Secondly, for the two samples (the Trial Sample–TS and the Normal setting sample–NS) in which the estimates of use and cost of asthma-related health services were derived for the non-trial setting, we estimated the use and cost of certain asthma-related services by standardising the results to the Canadian asthmatic population using the age-gender specific results from our samples (for the cost-effectiveness measure). This was an attempt at adjusting for age and gender differences of the subjects used in the RCT from

asthmatics in the population of Canada. The estimates of use and cost of asthma-related health services which were derived for the TS were similarly standardised (for the cost-efficacy measure). This standardisation serves as another method of comparing use and cost of health services between the groups and the settings.

The implications of the differences of age and gender of the subjects of the RCT from the subjects in real life on the generalisation of cost estimated in the RCT to that in real life is also discussed.

7.1 Methodology

7.1.1 Comparison of costs of anti-asthma health services during a clinical trial (for cost-efficacy) and the costs in non-trial subjects in a normal setting (for cost-effectiveness)

The analysis involved the subjects of the TS for which all required asthma-related health services information was available during at least a portion of the relevant period (71 during the clinical trial period, and 75 during the non-trial period), and the 51 subjects of the NS for which that same health services information was available.

The variable of total costs of anti-asthma health services used (annualised total cost for the trial period for the TS, and of course, for the non-trial period for the NS) was first increased for each subject by the same amount ($100) and transformed into base 10 Log, as the variable was non-normally distributed. The influence of group (TS vs. NS) on this transformed total cost

variable was analysed by way of least squares linear regression analysis.[1] The variable of average net yearly costs (total costs excluding the costs of iCSTs), also non-normally distributed, was reclassified into categories[2] of under $250 per year, or $250 or more, and the effect of independent variables were tested by way of log linear regression analysis.

The influence of the independent variables of age, gender, location, severity of asthma, presence of major comorbidities, and year of data (1995 or 1996; 1990 through 1994)[3] were tested on these outcome variables by simple regression, and those found to be significant ($p<0.15$) were then entered with the group variable in multiple regression analyses to estimate the adjusted results.

7.1.2 Estimated use and cost of asthma-related health resources by age and gender, adjusted for age-gender using the estimated Canadian asthmatic population as the reference population

Additionally, the study estimated use and costs of various categories of asthma-related health services, and the results were normalised by age and gender group to the Canadian asthmatic population.

Average daily quantities of inhaled corticosteroïds and inhaled beta-agonists, overall anti-asthma costs and costs for anti-asthma medications results were

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[1] The linear regressions were conducted using the SPSS version 7.5.1. The independent variables having been seen as significant were forcibly entered.

[2] The cut off point of $250 was chosen as it was close to the mode of the variable, and resulted in a frequency of nearly 50% of the 122 subjects in each group (63 higher; 59 lower).

calculated separately for six age-gender subgroups as follows: Men aged 20 to 44, 45 to 59, and 60 and over, and Women aged 20 to 44, 45 to 59, and 60 and over. The proportion of asthmatics in each of these sub-groups was estimated using the results of the 1996-97 National Population Health Survey, based on self-report in answer to the question, "I'd like to ask about certain chronic health conditions which you may have. We are interested in "long-term conditions" that have lasted or are expected to last 6 months or more and that have been diagnosed by a health professional." The prevalence rate of asthma estimated (Wilkins, 1999) is found in Table 7.1.

Certainly we are making a large, and likely unjustified assumption, that the population which we have sampled, those taking iCSTs and having mild to severe, but stable, asthma, are distributed according to age and gender groups in the same way as the overall asthmatic population in Canada.

Table 7.1 Prevalence of asthma and proportion of Canadian adult population aged 20-79.

Age and gender group	Prevalence of asthma*	Percentage of adults 20-79†
Men		
20-44	5.5%	24.7%
45-59	3.6%	7.0%
60 and over	5.2%	7.3%
Women		
20-44	8.4%	37.1%
45-59	6.9%	13.5%
60 and over	6.3%	10.4%

* 1996-97 National Population Health Survey
† 1996 Census of Population for Canada

[3] These variables are the same as used for the analysis in Chapter 5.

These prevalences were then adjusted for the age and gender make-up of the Canadian population (Table 1) from the 1996 Census of Population for Canada (Statistics Canada, 1999).

7.2 Results

7.2.1 Comparison of costs of anti-asthma health services during a clinical trial (for cost-efficacy) and the costs in non-trial subjects in a normal setting (for cost-effectiveness)

In a log regression analysis controlling for gender and geographic location (Montreal or Quebec City), the TS were less likely to have higher ($250 or more) average net yearly costs (total asthma related costs excluding the costs of iCSTs) than the NS (OR 0.3, 85%CI 0.2 – 0.5). The resulting model is as follows:

$$\text{Probability to have costs of \$250 or more} = 1 / 1 + e^{-z}$$

Where $z = 0.27 - 0.95Gr - 1.19G + 0.97T$

Gr = Group (1=TS, 0=NS)

G = Gender (1=Men, 0=Women)

T = Location (1=Montreal, 0=Quebec)

In a simple regression analysis exploring the effect of the independent variable of group (TS = 1, NS = 0) on the log transformed total asthma related costs, there was no significant difference between the two groups (p=0.29), but the slope was positive (Base 10 log of total costs = 4.75 + 0.06 Group). In a multiple regression analysis, log transformed total asthma related costs did not

differ significantly from the TS to the NS, controlling for age, severity of asthma and year. The resulting model[4] is as follows:

Base 10 log of (total costs + \$100 = 4.33 + 0.35*Gr*

+ 0.004*A* + 0.24*S* + 0.13*Y* + *e*

Where

Gr: = Group (1=Trial; 0=Normal Setting)

A: = Age in years in 1996

S: = Severity (1=severe; 0=mild, moderate)

Y: = Year (1=1995 or 1996; 0=1990 to 1994)

e: = error term

[4] The adjusted R-squared of the model is 0.146.

Table 7.2 Average annual costs of antiasthma medications, emergency room visits, ambulatory physician visits, hospitalizations and total costs, Trial sample, non-trial period.

	Age 20-44 n=28 Ave (SD)	Age 45-59 n=24 Ave (SD)	Age 60-79 n=23 Ave (SD)	Male n=28 Ave (SD)	Female n=47 Ave (SD)	All n=75 Ave (SD)	Normalised* Ave (SD)
Average annual cost of:							
Ambulatory physician visits	$130 (115)	$142 (132)	$194 (234)	$143 (134)	$159 (182)	$153 (156)	$144 (140)
Anti-asthma medications	$359 (347)	$504 (500)	$508 (378)	$449 (479)	$452 (371)	$451 (411)	$415 (384)
Emergency department	$101 (219)	$32 (156)	$59 (133)	$55 (141)	$73 (196)	$66 (177)	$89 (201)
Asthma hospitalization	$110 (581)	$4 (22)	$364 (1599)	$278 (1449)	$80 (458)	$154 (952)	$157 (534)
Total costs save iCSTs	*$496 (828)*	*$369 (309)*	*$775 (1698)*	*$656 (1553)*	*$473 (667)*	*$541 (1079)*	*$520 (875)*
Total costs	*$700 (836)*	*$682 (574)*	*$1124 (1721)*	*$924 (1609)*	*$765 (727)*	*$824 (1131)*	*$771 (939)*
Average daily use of :							
Inhaled Corticosteroids (mcg)	375 (450)	545 (585)	599 (542)	494 (620)	501 (470)	498 (527)	450 (494)
Short-term beta-agonists (puffs)	1.7 (2.5)	1.8 (2.1)	2.5 (2.4)	1.6 (1.8)	2.2 (2.6)	2.0 (2.4)	1.9 (2.4)
Average annual use of :							
Ambulatory physician visits	4.9 (4.6)	5.0 (4.5)	7.0 (7.8)	5.7 (5.3)	5.5 (6.0)	5.6 (5.8)	5.3 (5.2)

* Adjusted for age and gender group to the asthmatic Canadian population for 1996-97.

Table 7.3 Average annual costs of antiasthma medications, emergency room visits, ambulatory physician visits, hospitalizations and total costs, Normal Setting sample

	Age 20-44 n=22 Ave (SD)	Age 45-59 n=7 Ave (SD)	Age 60-79 n=22 Ave (SD)	Male n=8 Ave (SD)	Female n=43 Ave (SD)	All n=51 Ave (SD)	Normalised* Ave (SD)
Average annual cost of:							
Ambulatory physician visits	$164 (156)	$79 (122)	$213 (180)	$50 (55)	$197 (170)	$174 (166)	$155 (153)
Anti-asthma medications	$292 (410)	$245 (338)	$442 (513)	$167 (136)	$384 (479)	$350 (449)	$309 (414)
Emergency department	$110 (221)	$81 (215)	$147 (215)	$0 (0)	$144 (227)	$122 (215)	$95 (170)
Asthma hospitalization	$0 (0)	$0 (0)	$97 (234)	$0 (0)	$50 (172)	$42 (159)	$10 (24)
Total costs save iCSTs	*$452 (323)*	*$297 (322)*	*$625 (603)*	*$181 (134)*	*$566 (488)*	*$505 (472)*	*$451 (372)*
Total costs	*$566 (461)*	*$406 (444)*	*$899 (765)*	*$217 (152)*	*$775 (646)*	*$688 (629)*	*$592 (511)*
Average daily use of :							
Inhaled Corticosteroids (mcg)	207 (367)	204 (325)	485 (685)	75 (124)	373 (569)	327 (535)	256 (415)
Short-term beta-agonists (puffs)	3.1 (3.6)	2.2 (3.2)	2.5 (3.5)	1.8 (1.9)	2.9 (3.6)	2.7 (2.5)	2.8 (3.5)
Average annual use of :							
Ambulatory physician visits	6.6 (5.9)	3.7 (5.1)	8.7 (7.2)	2.3 (3.3)	8.0 (6.6)	7.1 (6.5)	6.4 (6.0)

* Adjusted for age and gender group to the asthmatic Canadian population for 1996-97.

Table 7.4 Average annual costs of antiasthma medications, emergency room visits, ambulatory physician visits, hospitalizations and total costs, Trial sample, trial period.

	Age 20-44 n=27 Ave (SD)	Age 45-59 n=23 Ave (SD)	Age 60-79 n=21 Ave (SD)	Male n=27 Ave (SD)	Female n=44 Ave (SD)	All n=71 Ave (SD)	Normalised* Ave (SD)
Average annual cost of:							
Ambulatory physician visits	$83 (141)	$98 (96)	$89 (107)	$73 (101)	$100 (125)	$90 (117)	$88 (126)
Anti-asthma medications	$622 (226)	$912 (423)	$886 (444)	$720 (354)	$839 (404)	$794 (387)	$727 (274)
Emergency department	$39 (141)	$21 (72)	$46 (115)	$33 (122)	$37 (109)	$35 (113)	$39 (124)
Asthma hospitalization	$7 (38)	$0 (0)	$0 (0)	$0 (0)	$4 (29)	$3 (23)	$5 (21)
Total costs save iCSTs	*$202 (241)*	*$302 (266)*	*$356 (334)*	*$205 (245)*	*$325 (298)*	*$280 (283)*	*$245 (250)*
Total costs	*$752 (311)*	*$1031 (447)*	*$1030 (499)*	*$826 (372)*	*$980 (461)*	*$922 (433)*	*$859 (343)*
Average daily use of :							
Inhaled Corticosteroids (mcg)	1059 (400)	1383 (530)	1288 (439)	1139 (470)	1289 (470)	1232 (472)	1184 (407)
Short-term beta-agonists (puffs)	1.0 (1.0)	1.5 (2.8)	1.3 (1.4)	1.0 (1.1)	1.3 (2.3)	1.2 (1.9)	1.1 (1.5)
Average annual use of :							
Ambulatory physician visits	3.7 (8.2)	4.3 (4.1)	3.7 (4.1)	3.3 (4.5)	4.2 (6.7)	3.9 (5.9)	3.8 (6.6)

* Adjusted for age and gender group to the asthmatic Canadian population for 1996-97.

7.2.2 Estimated differences of use and cost of asthma-related health resources adjusted for age-gender to the estimated Canadian asthmatic population

Table 7.2 contains the group-specific results for age groups and gender for the TS during the non-trial period, together with the overall results standardised for gender and age group using the estimated 1966 Canadian population of asthmatics as a reference. Table 7.3 contains the same information for the NS, and Table 7.4 for the TS during the trial period. When we adjusted for age and gender as indicated, costs for the average adult asthmatic (mild to severe) never enrolled in a clinical trial, prescribed inhaled corticosteroids, was estimated at $592 in the normal setting in 1996, and costs for the average adult asthmatic (again mild to severe) chosen to participate in a clinical trial was estimated at $771 per year, again in the normal (non-trial) setting. These are considerably less (although not significantly) than the figure estimated for the TS during the trial period: $859 per year.

In these results, we have made a crude attempt to compensate for the difference between the two groups and measures which could be accounted for by the differences in age and gender of the TS and the NS. The total costs for asthma treatment which were estimated in the age-gender adjusted TS in the trial setting are still higher than that same group in the normal setting, and again higher than the NS. Following the analyses from the two previous chapters, this is probably largely due to the high use and consequent

high cost of iCST in the RCT. The treatment construct differences are again very evident, even when the subject construct differences have been reduced.

The results of the total costs net of iCST are very different. The adjusted total cost net of the treatment drug were estimated at $520 (in the TS in the non-trial setting) and $451 (in the NS) again considerably higher, and this time significantly so[5], than the estimated $245 in the TS in the trial setting. Again we see the influence of the RCT construct and the difficulties this casts on the ability to generalise this measure of cost to the non-trial setting, even when some of the subject construct differences have been removed.

As expected, even adjusting for age and gender differences, the TS had lower total costs net of iCST in the trial setting than in the normal setting. However, those of the NS were lower than the TS when both groups were adjusted for age and gender. Our NS men appeared to have unusually low annual anti-asthma medication costs, and may not be representative of the true population. The men and women in the TS had similar costs, and the women in the NS had higher costs than the women in the TS. An explanation is that the TS were more severely asthmatic than the NS, as was hypothesised in Chapter 6, and this is reflected in the greater use of asthma resources, particularly when differences of age and gender between the two groups are controlled for. It is this latter hypothesis which may be more convincing,

[5] T-test, $p<.10$

particularly as these costs appear to be lower in all age groups in the NS than the TS. Additionally, although the costs of physician visits and emergency visits are higher in the NS, the costs of anti-asthma medications and hospitalisations are lower than the TS. This is consistent with a better controlled, but more severe, disease in the TS, although the number of hospitalisations in the sample is too low to be useful. But again the TS has both a higher daily use of iCST and a lower daily use of rescue bronchodilators, which is consistent either with this explanation, or that the TS is not more severe, but is more compliant.

7.3 Conclusion

With statistical analysis alone, it is difficult to generalise use of anti-asthma services estimated from the trial setting to the real life setting. Using regression analysis, the estimate of the total cost excluding that of iCSTs were higher in real life than in the clinical trial. Cost of iCSTs in the trial setting is higher than in real life, because the use is so much higher. But, because the other costs were lower in the trial setting, they compensated for the difference in iCST costs which were in the opposite direction, and we were unable to demonstrate any significant difference in the estimate of the total of asthma-related health services from the clinical trial to 'real life'. We may be seeing the effect of substitution of one type of treatment for another.

Economic evaluations have used total anti-asthma costs in calculations of cost-efficacy. Given our study results, simply generalising these results for the purposes of estimating cost-effectiveness would not be misleading. But the problem is that in the case of asthmatics taking iCSTs, the differences in the major components between the trial and the normal setting go in opposite directions, with the iCST cost decreasing from the trial setting to the normal setting and the other costs increasing.

The problems of generalisation result from differences not only in subject age and gender. As discussed in the previous chapters it also arises from other components of the subject construct: the fact of having been chosen for the trial, learning from the trial, and from being in the trial situation; from the setting construct difference (the cost of the different treatments to the patient), and the treatment construct difference. It may also result from the interaction of the iCST treatment with these construct differences.

Chapter 8

Discussion and Conclusion

This thesis has dealt with certain aspects of the pharmacoeconomics of asthma, specifically, the issue of the construct (external) validity of cost measurement during clinical trials (RCTs) using the example of inhaled corticosteroid (iCST) treatment for that disease.

The social sciences literature dealing with external, or construct validity of the RCT provided the theoretical framework to explore the implications of taking the use and cost of health services measured during the RCT, for the purposes of estimating cost-efficacy, and applying them to estimates of cost-effectiveness.

In this concluding chapter, we will present an overview of the results obtained pertaining to our initial questions, then discuss the overall impact of the work of our thesis, and conclude with some suggestions for future direction.

8.1 Questions posed and answered

Given that we cannot easily generalise the measures of use and cost of health services from the RCT to those in real life, what does the literature tell us of the factors that are responsible for differences in those measures, and how they can be better understood?

Our review of the literature shows that the following factors are included among those that influence the use of services and the associated costs of iCST treatment for asthma in real life:

1. physician (speciality),
2. patient (age, gender, risk attitude, interest and belief in the disease and its treatment), and
3. social system (availability and cost of alternative treatments).

The extent to which the effect of those factors are modified or diminished in the context of the RCT has been largely unexamined, although often discussed. This raises the question of the construct validity of the RCT. An RCT studying the effect of an iCST or any anti-asthma medication which is intended to be used on an ongoing basis is generally of short duration (usually less than 6 months), whereas the disease of asthma lasts normally many years or decades. The treatment construct of the RCT has limited flexibility in terms of dose and timing of the medication. The subjects are followed closely by a team of professionals, and the patients' symptoms and the difficulties they encounter controlling their asthma are given considerable attention by a professional (usually a nurse specialised in asthma care). The subjects know that they can phone if problems develop, and their questions will be answered promptly. They also must account, at least verbally, for all the medications

used to treat their asthma. All of these factors are different from real life asthma treatment, and the RCT produces a form of treatment which is different from that in real life, and different from the drug treatment alone.

The characteristics of the patients who are the subjects of clinical trials involving iCSTs for asthma may also differ considerably from the characteristics of subjects in real life, consequently the control of the disease and thus the effect of the treatment and the utilisation of health services and the costs associated could also differ. The age, gender, and asthma severity of the average trial subject may not be the same as that of the general population which would be treated by the anti-asthma medication. The trial subjects are usually selected for certain characteristics, including a lack of comorbidities, a history of stable disease, and their compliance to treatment. The demographic and disease characteristics of the subjects can be investigated in epidemiological studies, but the other characteristics which influence compliance may be much more difficult to examine. We could hypothesise that capacity to learn and control treatment, the ability to report symptoms, the tendency to ask for a referral to a specialist, may all contribute to differentiate the trial subject.

The literature had supported the hypothesis that the characteristics of the subject, the practitioner, and the social system combine to influence the use of health services for the treatment of asthma. As these factors are different in real life than in an RCT it is to be expected that the cost will differ in these two contexts. In this exploratory study, we investigated these differences. We

looked not just at the differences which could be accounted for by population demographics, but additionally at those found in the RCT inclusion and exclusion criteria which have not been the subject of the usual epidemiological studies.

The main outcome of interest looked at was the costs of asthma-related health services. Two main elements comprise these total asthma-related health services costs: the cost of the asthma treatment itself (in this case the iCST) and the costs associated with the consequences of the treatment, which include the costs to control the asthma and its symptoms, and the costs of monitoring the patient and the progress of the disease. It is for this reason that we estimated the total costs of asthma–related health services in two ways, as a total (of medications, physician visits, emergency visits and hospitalisations) and as a total net of the cost of iCSTs (the treatment itself).

What is known about pharmacoeconomics in asthma in the published literature and what are the important aspects of the chronic disease of asthma which pose particular problems for pharmacoeconomic analysis?

A thorough review of the literature has shown that the main characteristics of the disease of asthma which impact on pharmacoeconomic studies are:

1. it is a chronic disease which, in a majority of patients, affects morbidity and quality of life rather than mortality,
2. major exacerbations requiring costly hospitalisations are relatively rare in most subjects, and

3. compliance to anti-inflammatory medication has an important influence on the control of the disease.

Because of the need to measure morbidity and quality of life, the proposition of episode-free days as a measure of effect that can be used to compare treatments has been an important development. However, episode-free days have not yet been standardised, and the way they are defined may vary from one study to another – precluding easy comparison. The literature also has demonstrated the importance of the impact of hospital costs on the variation in cost measurement.

There has been no work we know of done in the area of disease measures that are useful for comparing asthma treatments to other healthcare interventions. The best current candidate again seems to be the episode-free day, which could prove useful to compare asthma with other chronic diseases which affect morbidity and quality of life (such as arthritis, migraine, and perhaps diabetes). A common definition, however, would be necessary (for example, in moderate chronic disease a day without symptoms could be used, or a day without the disease disturbing normal routine). Quality of life measures, in particular those measures which are common to other diseases (generic rather than disease-specific tools), have not been investigated either. The chronic nature of the disease, and the fact that non-severe asthma affects overall health status in a way difficult to detect with generic instruments means

that instruments which are often designed for short-term but debilitating disease conditions are less appropriate. The development of instruments more appropriate for chronic illness, which can reliably and validly detect smaller changes in life-quality over longer periods is important.

The wide variation of estimated cost-effectiveness measurements seen in the published literature also poses a problem for decision-makers. In addition to the methodological problems of certain studies, there is inconsistency in the effect measures and in the costs which do not allow for comparison between studies.

Again because of the chronic nature of the disease, the usefulness of short-term clinical trial information to assess the economic impact of a treatment such as iCST is questionable. In addition to its chronic nature, the importance of the adherence to iCST treatment regimens to control the disease implies that trial-based information may be difficult to translate to normal treatment conditions and to the wide variation in the population encountered in clinical practice.

How do the use and cost of asthma-related health resources measured in the same individual differ between the RCT and real life?

Overall anti-asthma costs in our exploratory study in a group of relatively well-controlled, mild to severe asthmatics, were higher in the trial setting than the normal setting. The treatment costs are largely due to the costs of iCSTs. As

the quantity taken of iCSTs was considerably higher in the trial setting than in the normal setting, the average cost was consequently much higher. On the other hand, there were, in the trial setting, lower average costs for all other asthma related health services.

The study showed how difficult it could be to generalise the results of RCT measured use and cost of asthma-related health services to real life, even using the same individuals. The study surmised that the treatment and setting constructs were sufficiently different between the RCT and real life to have a real impact on use and cost estimates. The RCT constructs may also interact with the drug treatment to produce the effect seen on the use and cost of health services.

We did, however, see some differences which could be measured statistically from the RCT to real life in the same subjects. Generalising from these observations, costs measured during the trial which excluded the iCST as the treatment under review would underestimate those costs in the normal setting. If total costs were considered, the opposite would be true, and the normal setting costs would be overestimated by the cost measured during the clinical trial.

We cannot truly talk about compliance to the medication regimens, but higher doses of iCSTs and lower doses of rescue bronchodilators could be explained

by better compliance or the prescription of more adequate treatment. The relationship between the dose of iCST therapy and other anti-asthma health costs has been borne out by this study. In general, for the period when the subjects are taking higher doses of iCSTs, their use of other resources to treat their disease is lower. However, when the use and cost of iCST is considered, the effect of lower 'compliance' could be to decrease rather than increase total anti-asthma costs. We must be very cautious in the conclusions we can draw from statistical comparisons of this very complex relationship of RCT construct and treatment. However, if the tendency seen in this preliminary study holds true for larger populations, the real life economic impact of iCST therapy overall is not underestimated by clinical trials, and the assessment of its positive economic impact may be in fact conservative.

The RCT works to reduce the influence of the individual characteristics of the patient on the effect of the iCST treatment, which may lead to the conclusion that there is an interaction between the RCT construct and that treatment. We saw, in general, that the demographic characteristics (age, gender, geographic location) of the subjects influenced total costs more during the non-trial period than during the trial period. Age was seen in the clinical trial subjects to influence total cost during the non-trial period, but not during the trial period, and was also seen as an important control variable when exploring the total non-trial period costs of the two subject groups. Gender was similarly important to explain the variation in cost in the trial group during the non-trial

period, but not during the trial period. Severity of asthma was an explicative variable with respect to total costs in both the trial and non-trial situations. The presence of major comorbidities was not seen as significant to total cost variation; this appears to confirm our choice of the elements of the cost of asthma-related health services.

The type of physician speciality, either general practitioner or specialist (pneumologist, or in very few instances, internal medicine specialists) was the only physician-associated variable which was used in the analyses. It was found not to influence the variation in costs, using the level of significance appropriate to our exploratory study, but if the direction of difference is examined, it was more associated with a variation in costs in the non-trial period than in the trial period.

We also saw an important difference associated with the geographic location of the subject in both the settings for the trial subject. It seems that in our trial group the more costly subjects are found in Montreal when compared to Quebec City. This is rather difficult to interpret, however, because the location was highly correlated with all the other variables which explained the variation of total costs. It could reflect a difference in the availability of services for the subjects, but these cities are not too different in the availability of and proximity to university and research level hospital facilities. There may be a difference in practice patterns between the two locations, but again, the

correlation with the other explanatory variables makes an interpretation difficult. A further exploration of this relationship would require much larger samples.

We can conclude, however, that the differences seen in subjects and practitioners influence the variability of costs in the normal setting. The presence of the protocol in the trial situation reduces the influence of these variables almost uniformly.

The conclusions of the study and the types of analyses we could perform were limited. The measures of severity, comorbidity and use of medications are all proxies for 'real' values. Recruiting TS subjects from already-completed RCTs reduced the response rate considerably, particularly for the older studies. The fact that pharmacists keep records for a limited period also curtailed the number of subjects in which we were able to estimate the use of total asthma-related health services. The resulting sample size was very small for studying costs, which are highly variable.

How does having been chosen as a subject and having participated in an RCT impact on the measurement of the use and cost of asthma-related health resources?

This study focussed on an aspect of the subject construct of the RCT which could explain the difficulties of generalising use and cost measured during that RCT. Our case study showed that even when controlling for the differences in

demographics, the use and cost of certain types of asthma-related health services differed between the subject of a clinical trial and a subject who had never participated in a trial. We speculated the difference was accounted for by having been so selected and having learned something from trial participation. We probably underestimated the effect of learning from the RCT by measuring the non-trial use of health services in some of the TS subjects prior to the trial period. The underestimation was probably not too important, as the investigators indicated that most of the subjects had been involved in previous asthma RCTs.

The difference in use of certain types of health services could also be due to a difference in the attitude of the subject to his or her asthma and its control, to the medication, to the advice of his or her health professional. There could be a difference in severity of the disease which was unaccounted for by the severity index (using as a proxy the medications prescribed).

Our study could detect no difference in overall use of asthma-related health services in individuals taking inhaled corticosteroids for their asthma, whether or not they had been enrolled in a clinical trial, but there was a large difference in the variance of the use of these services between the two groups. However, use of certain categories (including iCSTs, emergency department physician services, and general practitioner physician services) differed. Interpreting to real life from trial situations, we should expect to see a larger variance in the

use and cost of health services, a greater use in real life of the services of general practitioners, and a lower use of specialists, a lower use of inhaled corticosteroid therapy, and a concomitant greater use of 'rescue' medications.

The differences of use and cost were evident in subjects who were part of the clinical trial 'pool' even outside of the trial situation. If the learning experience of the trial is partially responsible for this difference, it is an encouraging sign for the value of education in asthma on treatment. It is also in concordance with the literature on asthma education which tends to find a positive impact on measured outcomes (for example, Anon., 1994).

The comments concerning the limitations of the study with respect to measures and samples made in the previous section can be repeated here. Additionally, the difficulties of recruiting 'comparable' asthmatics for the NS, without a physician assessment of disease and severity, and needing historical information on the use of medications sharply limited the NS sample size.

What is the difference between the use and cost of asthma-related health resources measured in a group of clinical trial subjects in an RCT and those resources measured in real life in a group of subjects who have never participated in a trial?

Overall anti-asthma costs in our exploratory study of relatively well-controlled, mild to severe asthmatics, contrasting the clinical trial subject in the trial

setting with the non-trial subject in the non-trial setting, did not differ significantly.

Economic evaluations have used overall (total) anti-asthma costs in calculations of cost-efficacy. At first view, given our study results, generalising these results for the purposes of estimating cost-effectiveness would not be misleading. However, depending upon the impact of the treatment therapy and the proportion of the total cost it represents, there may be some generalisation problems, as is demonstrated by our estimate of significantly higher costs during real life than during the clinical trial, when the treatment costs (in this case the cost of the iCSTs) are excluded. In a logistic regression analysis controlling for gender and geographic location (Montreal or Quebec City), the TS were less likely to have higher ($250 or more) average net yearly costs (total asthma related costs excluding the costs of iCSTs) than the NS (OR 0.3, 85%CI 0.2 – 0.5). It needs to be repeated, however, that these statistical results are not easily simply applied to translate the RCT measures to real life, given the discussions of the construct differences. This can be further seen when the estimates of use and cost are age- and gender-adjusted.

What are the differences between the average use and costs of asthma-related health resources, estimated from the RCT and from real life, adjusted for age and gender to an index population: the Canadian asthmatic population?

When we adjusted the estimates of use and cost in our study populations for age and gender group using an index population as a reference, we estimated that the cost of asthma-related health resources used annually by subjects never enrolled in a clinical trial, as approximately $592 in the normal setting. By comparison, the costs for similar persons again in the non-trial setting, but who had participated in a clinical trial was estimated at $771 per year. These are less (although not significantly so) than the figure, $859 per year, which was estimated for the trial setting.

If the cost used was net of iCST cost (the treatment drug), the cost in the non-trial setting would be $520 (in the Trial sample) and $451 (in the Normal Setting sample). These are considerably higher, but this time significantly so, than the estimated $245 for Trial sample in the trial setting.

8.2 Overall impact of the thesis: what have we learned? In what ways does the construct validity of the RCT affect the capacity to generalise the measures of use and cost of health services from the RCT to real life?

Figures 8.1 and 8.2 reproduce the figure originally set forth in Chapter 1 outlining the comparisons made, adding the results seen in the exploratory comparisons of costs, after having adjusted for the differences in age and gender between the samples. Figure 8.1 displays the differences seen in the

estimates of total asthma-related health costs and Figure 8.2, the total cost net of iCSTs.

Figure 8.1 Influence of the randomised clinical trial setting on the total cost of health services in asthma: outline of the results of the 3 comparisons made

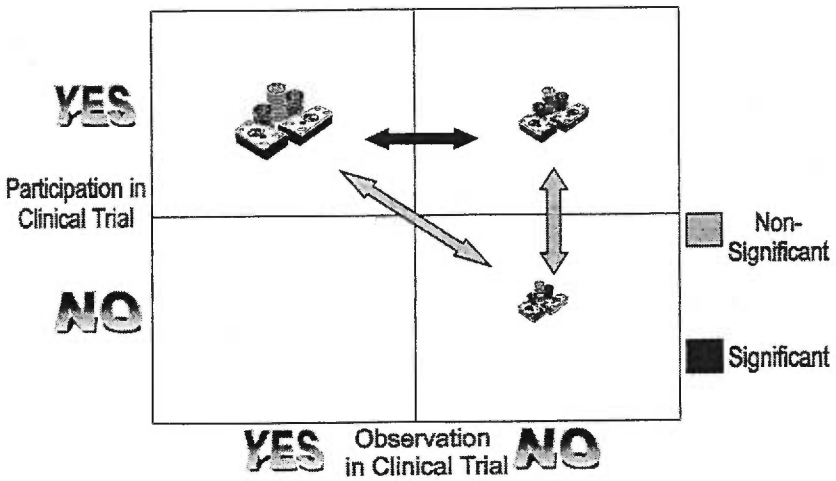
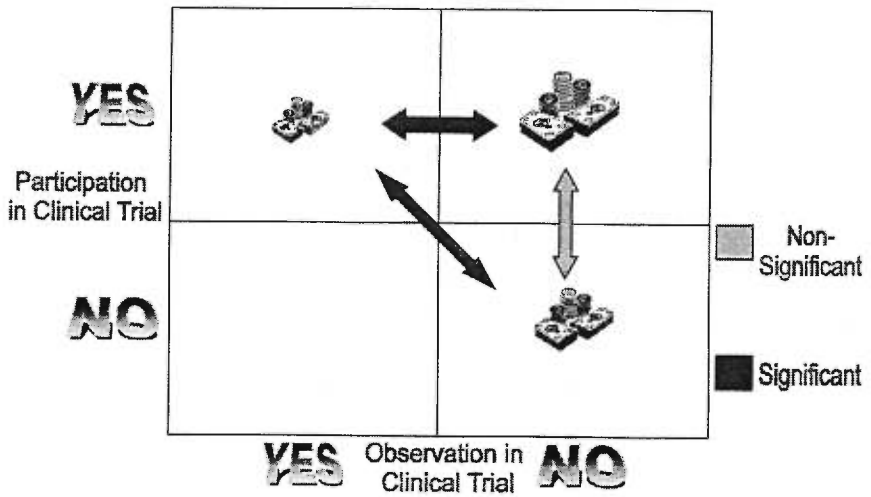


Figure 8.2 Influence of the randomised clinical trial setting on the total cost of health services in asthma *net of iCST costs*: outline of the results of the 3 comparisons made



With this age and gender adjustment, we made a crude attempt to control for subject construct socio-demographic differences from the RCT to real life, in order to focus on the differences which remain in the subject, treatment and setting constructs. We found that total costs for asthma treatment that were estimated in the age-gender adjusted TS in the trial setting are still higher than that same group in the normal setting, and again higher than the NS. Following the analyses from the two previous chapters, this is probably largely due to the high use and consequent high cost of iCST in the RCT. The influence of the treatment and setting construct differences are again very evident, even when the subject construct differences due to demographic factors have been reduced. And there is a likelihood of interaction with the

subject construct factors which remain: those which affect compliance behaviour.

The results of the total costs net of iCST are different in the opposite direction to total costs. This again points out that construct differences other than age and gender play and important role. We would therefore expect to see, in real life, a higher cost of asthma-related health services than that which would have been estimated from an RCT, if costs of the test medication (and its comparator, of course) were excluded.

The use and cost differences are consistent with the construct validity problems of the RCT. This includes the treatment construct. The controlled conditions of RCT, such as the need to report to the investigators and the need to record medication use in a daily diary, encourage better adherence to the anti-inflammatory medication, and a consequent lower need for the rescue medications. The close monitoring of the subject by the health care professionals responsible for the experiment, and the regular visits required by the protocol serve as a replacement for physician visits which would otherwise have occurred during normal conditions.

We noted also, in a few subjects in the trial group, the purchase of medications of the type only to be taken as supplied by the trial coordinators. We cannot conclude that these were taken in addition to the trial medication,

but certainly that possibility exists. This underlines the findings of other investigators who have cast doubt on the assumed high levels of adherence to protocols in clinical trials.

The construct differences also include the subject construct. Subject selection plays an important role in the explanation of these differences; selection for individuals who are adherent to their therapy would account for the higher use of anti-inflammatory medications seen under normal conditions in the group which had participated in the trial compared to the group which had not. With respect to other asthma related health services, the composition of the services differed between the two groups. Even controlling for age and gender differences, the fact of having been enrolled in an RCT and having participated is reflected in the differences seen in some types of services.

We must pose a series of questions on these otherwise hidden differences. Is the RCT subject more educated? (He or she must be able to pass the run-in period and comply with strict, and sometimes complex, treatment regimens, and very often must be able to keep patient diary records. If nothing more, this eliminates the non-literate portion of the population.) Is the subject more assertive and more interested in their disease? They are, after all, those individuals who are being followed by specialists, and in the normal course of treatment, this would require a referral from a general practitioner. Have they

learned from the trial experience? Have they learned from their physicians, who are more likely to be specialists in respiratory disease?

The study was unable to demonstrate a difference in total anti-asthma costs between the two groups, for three reasons. First the variance in total costs in the NS was so large as to demand larger sample sizes. Secondly, because we may have conservatively incorporated the learning effect of the RCT in the TS because a number of them may have not yet participated in an RCT when the measure was taken. Lastly, because the differences in the use and cost of anti-inflammatory medication balanced the difference which existed between the use of other asthma-related health services. However, the direction was consistent with the results from the separate analyses. An investigation in a larger group or other studies would be useful to confirm these preliminary findings.

The outcome measures of RCTs can include resource use and costs as measures of effect, and costs as the numerator for cost-effectiveness measures. Users of cost-effectiveness data are particularly interested in applying this information to real life situations. This study casts doubt on the ability of the RCT to provide use and cost information which can be used to in a modelling process to generate 'real life' data for cost-effectiveness studies.

The RCT construct, interacting with the iCST treatment, prohibits easy translation. We looked at the question in a small sample of moderate and severe, stable, asthmatics, but the same dynamic should certainly be seen in other chronic diseases. However, if RCT data were to be used in such a modelling process, our statistical analyses indicate that certain crude adjustments should be made. The dose and cost of iCST use measured under the influence of the protocol should be reduced for a model simulating normal conditions, and the use and cost of rescue medications and other asthma-related health services should be increased. For example, a certain augmentation in physician visits, for which the protocol visits have substituted, should be accorded when simulating real-life conditions. (However, if all RCT protocol-demanded visits had been incorporated into the treatment costs, the opposite should be done, as this would normally reflect a higher than normal number of health professional contacts.)

As a side-bar to this conclusion, the methods we used to recruit normal setting subjects in our study were found to have been somewhat problematic. Recruitment of ambulatory subjects by pharmacies using a diagnosis for selection was difficult. The lack of historical ambulatory drug use information also restricted the recruiting process. If a similar study was to be undertaken, it would seem more appropriate to use physician practices to recruit the normal setting sample, and save pharmacies to recruit subjects for studies requiring individuals selected on the basis of their use of specific medications.

It would also be appropriate not to underestimate the proportion of the population aged 45 or older who had smoked for over 20 years, which sharply limits the pool of potential eligible subjects.

8.3 Suggestions for future direction: where do we go from here?

This has been a small step exploring the difficulties of generalising the use and cost of health services from the clinical trial to normal use conditions. Recommendations for improving the construct validity of clinical trials in chronic diseases such as asthma have included the pursuit of studies over longer time frames, and the incorporation of real-life conditions and patient characteristics in studies evaluating cost-effectiveness of asthma treatments. Our analysis has cast doubt on the ability to compensate for the important problems of construct validity, and because of this, the importance of Phase IV trials using non-intervention methodology to generate cost-effectiveness information is confirmed.

Our study has not explored how the characteristics of the population of individuals who are treated with corticosteroids for asthma during clinical trials differ from those in the population treated in real life. This would require a sample representative of the normal setting population, which could then be compared to a trial sample. A larger-scale prospective study using a sample recruited from real life would be of interest, allowing an exploration of the

effect of subject demographic characteristics on the use of health resources in real life, when compared to subjects in the trial situation.

In addition, we are left with a series of related questions. What are the characteristics of the individual selected for the clinical trial which affect their use of health resources, particularly their adherence to drug treatment regimens? What is their understanding of and what are their attitudes towards the advice of health professionals? the importance of medications? the risks associated with their disease? the risks associated with drug therapy? Do those characteristics differ from the individuals never having been chosen for a trial?

Future studies in clinical trial and community populations of asthmatics, focussing on the subject's behavioural characteristics and attitudes are of interest to explore these questions of the influence of the RCT construct on health services use and cost measurements. Additionally, studies in populations with other chronic diseases such as migraine, diabetes and hypertension would be interesting in order to further explore the dimensions of the external (construct) validity of the RCT.

REFERENCES

Adams S, Pill R, Jones A. Medication, chronic illness and identity: the perspective of people with asthma. *Soc Sci Med* 1997; 45: 189-201.

Adelroth E, Thompson S. Advantages of high-dose inhaled budesonide. *Lancet* 1988; 1: 476.

Agertoft L , Pederson S. Cost-effectiveness of inhaled budesonide in children with chronic asthma (abstract). *Am J Respir Crit Care Med* 1997; 155: A351.

Alessandro F, Vincenzo ZG, Marco S, Marcello G, Enrica R. Compliance with pharmacologic prophylaxis and therapy in bronchial asthma. *Annals Allergy* 1994; 73: 135-40.

Altman LC, Findlay SR, Lopez M, Morris RJ, Lukacso P, Pinnas JL, Ratner PH, Szefler SJ, Wlch MJ. Adrenal function in adult asthmatics during long-term daily treatment with 800, 1,200, and 1,600 micrograms triamcinolone acetonide. Multicenter study. *Chest* 1992; 101(5): 1250-6.

American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Resp Dis* 1993;147:1056-1061.

Anderson R, Newman JF. Societal and individual determinants of medical care utilisation in the United States. *Milbank Memorial Fund Quarterly* 1973; 51: 95-124.

Anonymous. From research to practice. *The Lancet* 1994; 344: 417-8.

Anonymous. Integrated care for asthma: a clinical, social, and economic evaluation. Grampian Asthma Study of Integrated Care (GRASSIC). *BMJ* 1994; 308: 559-64.

Anonymous. International Consensus Report on the Diagnosis and Management of Asthma. *Clin Exper Allergy* 1992; 22: Supp 1.

Anonymous. Medicaments pour le traitement de l'asthme. *La Lettre Medicale* 1995; 18: 93-96.

Balkrishnan R, Norwood GJ, Anderson A. Outcomes and cost benefits associated with the introduction of inhaled corticosteroid therapy in a Medicaid population of asthmatic patients. *Clin Ther* 1998; 20: 567-580. (a)

Balkrishnan R, Norwood GJ, Anderson A. Effects of inhaled corticosteroid therapy introduction in asthmatic Medicaid-enrolled children. *Drug Benefit Trends* 1998; 10: 37-40. (b)

Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of iCSTs. *Am J Resp Crit Care Med* 1998; 157: S1-S53.

Barter CE Campbell AH. Relationship of constitutional factors and cigarette smoking to decrease in 1-second forced respiratory volume. *Am Rev Resp Dis* 1976; 113: 305-14.

Béland F. Introduire la durée dans la conception et la mesure de l'utilisation des services médicaux. *Ruptures* 1994; 1: 28-44.

Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? *Ann Allergy Asthma Immunol* 1997; 79: 177-186.

Blais L, Suissa S, Boivin JF, Ernst P. First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma. *Thorax* 1998; 53: 1025-1029.

Blais R. Variations in surgical rates in Quebec: Does access to teaching hospitals make a difference? *Can Med Assoc J* 1993; 148(10): 1729-36.

Bloom BS, Fendrick AM. Timing and timeliness in medical care evaluation. *Pharmacoeconomics* 1996; 9: 183-187.

Bolton MB, Tilley BC, Kuder J, Reeves T, Schultz LR. The cost and effectiveness of an education program for adults who have asthma. *Jour Gen Intern Med* 1991; 6(5): 401-407.

Booth PC, Capsey LJ, Langdon CG, Wells NEJ. A comparison of the cost effectiveness of alternative prophylactic therapies in the treatment of adult asthma. *Br J Med Econ* 1995; 8: 65-72.

Booth PC, Wells NEJ, Morrison AK. A comparison of the cost effectiveness of alternative prophylactic therapies in childhood asthma. *PharmacoEconomics* 1996; 10: 262-268.

Bosco LA, Gerstman BB, Tomita DK. Variations in the use of medication for the treatment of childhood asthma in the Michigan Medicaid Population, 1980 to 1986. *Chest* 1993; 104: 1727-32.

Bosco LA, Knapp DE, Gerstman B, Graham CF. Asthma drug therapy trends in the United States, 1972 to 1985. *J All Clin Immun* 1987; 80: 398-402.

Boulet L, Milot J, Beaupré A. Mortalité associée à l'asthme au Québec de 1975 à 1985. *Union Medicale du Canada* 1989; 150-157.

Bowton DL, Goldsmith WM, Haponik EF. Substitution of metered-dose inhalers for hand-held nebulizers success and cost savings in a large, acute-care hospital. *Chest* 1992; 101: 305-308.

Bregenzer T, Mossinger C, Medici TC. [Therapy changes and cost development in bronchial asthma. A 10-year retrospective study at the medical outpatient clinic of the Zurich University Hospital]. *Pneumologie* 1990; 44: 960-6.

Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ* 1994; 3: 95-104.

Broder I, Tarlo SM, Davies GM, Thomas P, Leznoff A, Sturgess J, Baumal R, Mintz S, Corey PN. Safety and efficacy of long-term treatment with inhaled beclomethasone dipropionate in steroid-dependent asthma. *Can Med Assoc J* 1987; 136(2): 129-35.

Bryan S, Buxton MJ. Economic evaluation of treatments for respiratory disease. *PharmacoEconomics* 1992; 2: 207-218.

Buxton MJ. The economics of asthma -- an introduction. *Eur Resp Rev* 1996; 6: 105-107.

Campbell DT. Relabeling internal and external validity for applied social scientists. *New Directions for Program Evaluation* 1986; 31:67-77.

Campbell DT and Stanley JC. Experimental and Quasi-experimental Designs for Research. Boston: Houghton Mifflin, 1963.

Campbell LM, Simpson RJ, Turbitt ML, Richardson PDI. A comparison of the cost-effetiveness of budesonide 400 µg/day and 800 µg/day in the management of mild to moderate asthma in general practice. *Br J Med Econ* 1993; 6: 67-74.

Canadian Coordinating Office for Health Technology Assessment. *Guidelines for economic evaluation of pharmaceuticals*. Ottawa. November 1994.

Chmelik F, Doughty A. Objective measurements of compliance in asthma treatment. *Annals of Allergy* 1994; 73: 527-32.

Christiaanse ME, Lavigne JV, Lerner CV. Psychosocial aspects of compliance in children and adolescents with asthma. *J Dev Beh Pediatrics* 1989; 10: 75-80.

Clark NM, Feldman CH, Evans D, Levison MJ, Wasilewski Y, Mellins RB. The impact of health education on frequency and cost of health care use by low income children with asthma. *J Allergy & Clin Immun* 1986; 78(1 Pt 1): 108-15.

Clark T. Mise à jour sur les recommandations du consensus. *le clinicien* 1994; November(Suppl): 7-11.

Cochrane GM. Therapeutic compliance in asthma; its magnitude and implications. *Eur Resp Jour* 1992; 5: 122-4.

Coffey E, Moscovice I, Finch M, Christianson JB, Lurie N. Capitated Medicaid and the process of care of elderly hypertensives and diabetics – results from a randomized trial. *Amer Jour Med* 1995; 98(6): 531-536.

Collet JP, Boissel JP (1991). Sick population--treated population: the need for a better definition. The VALIDATA Group. *Eur Jour of Clin Pharmacology* 41(4): 267-271.

Connelly JE, Philbrick JT, Smith GR, Kaiser DL, Weimer A. Health perceptions of primary care patients and the influence on health care utilization. *Med Care* 1989; 27 Suppl: S99-S109.

Connet JG, Lenney W, McConchie SM. The cost effectiveness of budesonide in severe asthmatics aged one to three years. *Br J Med Econ* 1993; 6: 127-134.

Conrad KJ, Conrad KM. Reassessing validity threats in experiments. Focus on construct validity. *New Directions for Program Evaluation* 1994; 63:5-25.

Conrad P. The meaning of medications: another look at compliance. *Soc Sc & Medicine* 1985; 20: 29-37.

Contandriopoulos AP. Réformer le système de santé: une utopie pour sortir d'un statu quo impossible. *Ruptures* 1994; 1: 8-26.

Contandriopoulos AP, Champagne F, Denis JL, Pineault R. L'Évaluation dans le domaine de la santé: concepts et méthodes. L'évaluation en matière de santé: des concepts à la pratique, Lille, 1992.

Contandriopoulos AP, Champagne F, Potvin L, Denis J-L, Boyle P. *Savoir préparer une recherche, la définir, la structurer, la financer.* Montreal: Les presses de l'Université de Montréal, 1990.

Cook TD, Campbell DT. *Quasi-experimentation Design & Analysis Issues for Field Settings.* Chicago: Rand McNally College Publishing, 1979.

Coyle D, Lee KM. The problem of protocol driven costs in pharmacoeconomic analysis. *Pharmacoeconomics* 1998; 14: 357-363.

Cronbach LJ. *Designing Evaluations of Educational and Social Programs.* San Francisco: Jossey-Bass, 1987.

Cunningham WE, Bozzette SA, Hays RD, Kanouse DE, Shapiro MF. Comparison of health-related quality of life in clinical trial and nonclinical trial human immunodeficiency virus-infected cohorts. *Medical Care* 1995; 33: AS15-AS25.

D'Agostino RB, Kwan H. Measuring effectiveness what to expect without a randomized control group. *Medical Care* 1995; 33: AS95-AS105.

Dahl, R., B. Lundback, Malo JL, Mazza JA, Niemenen MM, Saarelainen P, Barnacle H. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. International Study Group. *Chest* 1993; 104(5): 1352-8.

Davey P, Malek M. The impact of pharmacoeconomics on the practitioner and the patient. *PharmacoEconomics* 1994; 6: 298-309.

Deenen TAM, Klip EC. Coping with asthma. *Resp Medicine* 1993; 87 (Suppl B): 67-70.

Delfino RJ, Becklake MR, Hanley JA. Reliability of hospital data for population-based studies of air pollution. *Arch Environ Health* 1993: 48: 140-146.

Denson-Lino JM, Willies-Jacobo LJ, Rosas A, O'Connor RD, Wilson MW. Effect of economic status on the use of house dust mite avoidance measures in asthmatic children. *Annals of Allergy* 1993; 71(2): 130-2.

Deter HC. Cost-benefit analysis of psychosomatic therapy in asthma. *Journal of Psychosomatic Res.* 1986; 30: 173.

Diamond GA, Denton TA. Alternative perspectives on the biased foundations of medical technology assessment. *Annals of Int Med* 1993; 118: 455-464.

Donabedian A. *Benefits in Medical Care Programs.* Cambridge: Harvard University Press, 1976.

Drazen JM, Israel E. Treating mild asthma -- when are inhaled steroids indicated? *NEJM* 1994; 331(11): 737-8.

Drummond ME. The emerging government requirement for economic evaluation of pharmaceuticals. *PharmacoEconomics* 1994; 6(Suppl 1): 42-50.

Drummond ME, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd edn. Oxford: Oxford University Press, 1997.

Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care progammes*. Oxford: Oxford University Press, 1987.

Eisenberg JM. Physician utilization: the state of research about physicians practice patterns. *Medical Care* 1985; 25(5): 461-83.

Émond A, Guyon L, Camirand F, Chenard L, Pinealut R, Robitaille Y. *Et la santé, ça va? Tome 1, Rapport de l'enquête Santé québec 1987*. Québec: Publications du Québec, 1988.

Engel W, Freund DA, Stein JS, Fletcher RH. The treatment of patients with asthma by specialists and generalists. *Medical Care* 1988; 27: 306-312.

Ernst P, Fitzgerald JM, Spier S. Conférence canadienne de consensus sur l'asthme resumé des recommendations. *Can Respir J* 1996; 3: 101-114.

European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9: 687-695.

Evans III R, Mullally DI, Wison RW, Gergen PJ, Rosenberg HM, Grauman JS, Chevarley FM, Feinleib M. National trends in the morbidity and mortality of asthma in the US. Prevalence, hospitalisation and death from asthma over two decades: 1965-1984. *Chest* 1987; 91(Suppl): 65S-73S.

Fauroux B, Just J, Couvreur J, Grimfeld A, Tournier G. Connaissance et adhésion au traitement de l'asthme de l'enfant: résultats d'une enquête prospective. *Rev Pneumol Clin* 1992; 48(1): 12-8.

Fayers PM, Hand DJ. Viewpoint : Generalisation from phase III clinical trials : survival, quality of life, and health economics. *Lancet* 1977; 350: 1025-1027.

Feinstein AR. Problems, pitfalls, and opportunities in long-term randomized trials. *Drug Research and Drug Development in the 21st Century*, Bayer, AG Centenary Sumposium, 1988.

Fireman P, Firday GA, Gira C, Vierhaler SW, Michaels L. Teaching self-management skills to asthmatic children and their parents in an ambulatory care setting. *Pediatrics* 1981; 68: 341.

Fleiss JL. *Statistical Methods for Rates and Proportions.* 2nd edn. 1981 New York: John Wiley & Sons.

Freund DA, Dittus RS. Principles of Pharmacoeconomic Analysis of Drug Therapy. *PharmacoEconomics* 1992; 1: 20-31.

Freund DA, Stein J, Hurley R, Engel W, Woomert A, Lee B. Specialty differences in the treatment of asthma. *J Allergy & Clin Immun* 1989; 84(3): 401-6.

Gerdtham UG, Hertzman P, Boman G, Jönsson B. Impact of inhaled corticosteroids on asthma hospitalization in Sweden. *Applied Economics* 1996; 28: 1591-1599.

Gergen PJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979-1987. *JAMA* 1990; 264: 1688-92.

Gerstman BB, Bosco LA, Tomita DK, Gross TP, Shaw MM. Prevalence and treatment of asthma in the Michigan medicaid population younger than 45 years, 1980-1986. *J Allergy & Clin Immun* 1989; 83: 1032-9.

Gibson P, Henry D, Francis L, Cruickshank D, Dupen F, Higginbotham N, Henry R, Sutherland D. Association between availability of non-prescription beta 2 agonist inhalers and undertreatment of asthma. *BMJ* 1993; 306(6891): 1514-8.

Gold MR, Patrick DL, Torrance GW, Fryback DG, Hadorn DC, Kamlet MS, Daniels N, Weinstein MC. Identifying and Valuing Outcomes. In: Gold MR, Seigel JE, Russell LB, Weinstein MC (eds) *Cost-effectiveness in Health and Medicine*. New York: Oxford University Press, 1996: 82-134.

Greer AL. The diffusion of new medical technologies into practice. *Int Jour Tech Assess Health Care* 1988; 4: 5-26.

Greineder DK, Loane KC, Parks P Reduction in resource utilization by an asthma outreach program. *Arch of Pediatr Adolesc Medicine* 1995; 149(4): 415-420.

Groot CA, Lammers JW, Molema J, Festen J, van Herwaarden CL. Effect of inhaled beclomethasone and nedocromil sodium on bronchial

hyperresponsiveness to histamine and distilled water. *Eur Resp Jour* 1992; 5(9): 1075-1082.

Group EuroQol. EuroQol: a new facility for the measurement of health-related quality of life. *Health Pol* 1990; 16: 199-208.

Hall JR, Miocevich MI, O'Neill BA, Wells NEJ. A comparison of the cost effectiveness of salmeterol v salbutamol in patients with moderate asthma. *Thorax* 1992; 47: 883.

Hallas J, Hansen NC. Individual utilization of anti-asthma medication by young adults: a prescription database analysis. *Jour Intern Medicine* 1993; 234: 65-70.

Hammersly M. Abording internal and external validity: a response to Swanburn. *Quality and Quantity* 1993; 27:217-218.

Hammersly M. A note on Campbell's distinction between internal and external validity. *Quality and Quantity* 1991; 25:381-387.

Hargreave F, Dolovich J, Newhouse M. The assessment and treatment of asthma: A conference report. *J Allergy Clin Immunol* 1990; 85:1098-1111.

Health Canada Communications and Consultation Directorate. *Report on the health of Canadians.* Ottawa: Minister of Supply and Serivces Canada. 1996.

Health Canada, Health Protection Branch – Laboratory Centre for Disease Control. *Respiratory Disease Division Facts and Figures.* Health Canada Internet Web Site www.hc-sc.gc.ca/main/lcdc/web/bcrdd/crd/burden/, 99-01-14, 1999.

Hendrick DJ. Asthma: epidemics and epidemiology. *Thorax* 1989; 44: 609-13.

Hershey JC, Baron J. Clinical reasoning and cognitive processes. *Med Dec Making* 1987; 7(4): 203-11.

Hodgkin JE. United States audit of asthma therapy. *Chest* 1986; 90(5 Suppl.): 62S-66S.

Holtgrave DR, Lawler F, Spann SJ. Physicians' risk attitudes, laboratory usage, and referral decisions: the case of an academic family practice center. *Med Dec Making* 1991; 11(2): 125-30.

Horn CR. The assessment of therapeutic compliance by asthmatic patients. *Eur Resp Jour* 1992; 5(1): 126-7.

Horn CR, Cochrane GM. Management of asthma in general practice. *Resp Medicine* 1989; 83: 67-70.

Infante-Rivard C, Esnaola S, Roberge D, Baumgarter M. The changing frequency of childhood asthma. *Jour of Asthma* 1987; 24: 283-8.

Jasper AC, Mohsenifar Z, Kana S, Goldberg HS, Koerner SK. Cost-benefit comparison of aerosol bronchodilator delivery methods in hospitalized patients. *Chest* 1987; 91: 615-618.

Jenkins MA, Hurley SF, Bowes G, McNeil JJ. Use of antiasthmatic drugs in Australia. *Med Jour Australia* 1990; 153: 323-8.

Johannesson M, Weinstein MC. Designing and conducting cost-benefit analyses. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 1085-1092.

Juniper EF, Guyatt GH. Asthma and Allergy. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials.* 2nd edn. Philadelphia: Lippincott-Raven, 1996: 977-982.

Juniper EF, Guyatt GH, Griffith LE. Measuring quality of life in asthma. *Am Rev Resp Dis* 1993; 147: 832-838.

Kaliner MA. Evolution of asthma treatments. *Annals Allergy* 1993; 71(3): 300-5.

Kaliner MA. How the current understanding of the pathophysiology of asthma influences our approach to therapy. *J Allergy Clin Immunol* 1993;92:144-147.

Kanji GK. *100 Statistical Tests.* New York: Sage Publications, 1993.

Keeler E, Brook RH, Goldberg GA, Kamberg CJ, Newhouse JP. How free care reduced hypertension in the health insurance experiment. *JAMA* 1985; 254: 1926.

Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med* 1994; 154(12): 1349-52.

Kesten S, Rebuck AS, Chapman KR. Trends in asthma and chronic obstructive pulmonary disease therapy in Canada, 1985 to 1990. *J Allergy Clin Immunol* 1993; 92: 499-506.

Kesten S, Rebuck AS. Asthma in New Zealand: Implications for North America. *Jour Asthma* 1991; 28: 193-9.

Kind P. The EuroQoL instrument: an index of health-related auality of life. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 191-201.

Koopmanschap MA, Rutten FFH. A practical guide for calculating indirect costs of disease. *PharmacoEconomics* 1996; 10: 460-466.

Kraemer HC, Thiemann S. How Many Subjects? *Statistical Power Analysis in Research*. Newbury Park, Sage Publications, 1987.

Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada, 1990. *CMAJ* 1996; 154:821-831.

Langley PC. Cost-effectiveness profiles with an expanding treatment population. *Clin Ther* 1995; 17: 1207-1212.

Larsson L, Boethius G, Uddenfeldt M. Differences in utilization of asthma drugs between two neighboring Swedish provinces: relation to symptom reporting. *Eur Resp Jour* 1993; 6: 198-203.

Laurier C, Kennedy W, Gariepy L, Archambault A, Contandriopoulos AP. *The use of anti-asthma medications and medical health services in the province of*

Quebec by persons with asthma. Montreal: GRIS, University of Montreal, 1994.

Laurier C, Kennedy W, Gariepy L, Archambault A, Contandriopoulos AP. *The use of anti-asthma medications in two Quebec populations of anti-asthma medication users: a prescription database analysis. Chron Dis Canada* 1997; 18(1): 20-26.

Laurier C, Kennedy W, Gautrin D, Ghezzo H, Paré M, Labbé D, Contandriopoulos AP. Rate and cost of hospitalisations for asthma in Quebec: an analysis of 1988-1995 data. Submitted to Chronic Diseases in Canada (February, 1999).

Leese B. The cost of diabetes and its complications. *Soc Sci Med* 1992; 35: 1303-1310.

Leufkens HG, Urquhart J. Variability in patterns of drug usage. *Jour Pharmacy Pharmacology* 1994; 46(Suppl 1): 433-7.

Lewis CE, Rachelefsky G, Lewis MA, de la Sota A, Kaplan M. A randomized trial of A.C.T. (asthma care training) for kids. *Pediatrics Patient Behavior* 1984; 74(4): 478-86.

Lockyer JM. Physician performance: the roles of knowledge, skill, and environment. *Teaching Learning Medicine* 1992; 4(2): 86-96.

Lofdahl CG. Cost development of obstructive airway disease in Sweden. *Eur Resp Rev.* 1996; 6: 113-115.

MacKinnon NJ, Flagstad MS, Peterson CR, Mesch-Beatty K. Disease management program for asthma: baseline assessment of resource use. *Am J Health-Sys Pharm* 1996; 53: 535-541.

Maheux B, Dufort F, Beland F, Jacques A, Levesque A. Female medical practitioners: More preventive and patient oriented? *Med Care* 1990; 28(1): 87-92.

Mak H, Johnston P, Abbey H, Talamo RC. Prevalence of asthma and health service utilization of asthmatic children in an inner city. *Jour Allergy Clin Immun* 1982; 70(5): 367-372.

Malo JL, Martin J, Boulet LP. Asthma, an inflammatory disease: the resulting diagnostic and clinical methods. *Union Medicale Canada* 1991; 120(6): 448-54.

Manfreda J, Mao Y, Litven W. Morbidity and mortality from chronic obstructive pulmonary disease. *Am Rev Resp Dis* 1989; 140:S19-S26.

Manson A. Language concordance as a determinant of patient compliance and emergency room use in patients with asthma. *Med Care* 1988; 26(12): 1119-28.

Mao Y, Semenciw R, Morrison H, MacWilliam L, Davies J, Wigle D. Increased rates of illness and death from asthma in Canada. *CMAJ* 1987; 137: 620-4.

Marion RJ, Creer TL, Reynolds RV. Direct and indirect costs associated with the management of childhood asthma. *Annals Allergy* 1985; 54(1): 31-4.

Marks G, Dunn SM, Woolcock AJ. A scale for the measurement of quality of life in adults with asthma. *J Clin Epid* 1992; 45: 461-472.

Mawhinney H, Spector SL, Kinsman RA, Siegel SC, Rachelefsky GS, Katz RM, Rohr AS. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. *Annals Allergy* 1991; 66(4): 294-299.

Mayo PH, Richman J, Harris HW. Results of a program to reduce admissions for adult asthma. *Annals Intern Medicine* 1990; 112: 864-871.

Mayo NE, Danys I, Carlton J, Scott SC. Accuracy of hospital discharge coding for stroke. *Can Jour Cardiol* 1993; 9(suppl D): 121-124.

Mellis CM, Peat JK, Woolcock AJ. The cost of asthma Can it be reduced? *PharmacoEconomics* 1993; 3(3): 205-19.

Mellis CM, Peat JK, Bauman AE, Woolcock AJ. The cost of asthma in New South Wales. *Med J Aust* 1991;155: 522-528.

Milne RJ. Evaluation of the Pharmacoeconomic Literature. *PharmacoEconomics* 1994; 6: 337-345.

National Institutes of Health. *Guidelines for the diagnosis and management of asthma.* Expert panel report, No. 2. Bethesda: National Institutes of Health, (NIH Publication No. 97-4051), 1997.

Newhouse JP, Manning WG, Morris CN, Orr LL, Duan N, Keeler EB, Leibowitz A, Marquis KH, Marquis MS, Phelps CE, Brook RH. Some interim results from a controlled trial of cost sharing in health insurance. *N Eng J of Med* 1981; 305(25): 1501-1507.

Nolan B. Economic incentives, health status and health services utilisation. *Jour Health Econ* 1993; 12: 151-69.

O'Brien BJ. Efficacy v. effectiveness measures. Standards for economic evaluation of drugs: issues and answers. Chapel Hill, North Carolina, 1995.

O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Med Care* 1994; 32: 150-163.

O'Neill CJA, Dobbs RJ, Dobbs SM. Measurement of compliance with medication: the sine qua non of clinical trials in old age? *Age Ageing* 1991; 20(2): 77-79.

Osterhaus JT, Townsend RJ. Incorporating pharmacoeconomic research into clinical trials. In: Bootman JL, Townsend RJ, McGhan WF (eds) *Principles of Pharmacoeconomics*. 2nd edn. Cincinnati: Harvey Whitney Books Company, 1996: 196-211.

Pachter LM, Weller SC. Acculturation and compliance with medical therapy. *J Develop Behav Pediatr* 1993; 14(3): 163-8.

Pauley TR, Magee MJ, Cury JD. Pharmacist-managed, physician-directed asthma management program reduces emergency department vists. *Annals of Pharmacotherapy* 1995; 29(1): 5-9.

Pearson MG, Johnson FN. Pharmacoeconomic aspects of fluticasone propionate in the treatment of asthma. *Rev Contemp Pharmacother* 1998; 9: 591-599.

Perera BJC. Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country. *Arch Dis Child* 1995; 72 :312-316.

Podell RN. National guidelines for the management of asthma in adults. *Amer Fam Phys* 1992; 46: 1189-96.

Posnett J, Jan S. Indirect cost in economic evaluation: the opportunity cost of unpaid inputs. *Health Econ* 1996; 5: 13-23.

Price DB, Appleby JL. Fluticasone propionate: an audit of outcomes and cost-effectiveness in primary care. *Resp Med.* 1998; 92: 351-353.

Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, Li VC, Tashkin DP. Metered-dose inhaler adherence in a clinical trial. *Am Rev Respir Dis* 1992; 146(6): 1559-64.

Revicki DA. Relationship of pharmacoeconomics and health-related quality of life. In: Spilker B, (ed) *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 1077-1083.

Richards JM, Hemstreet MP. Measures of life quality, role performance, and functional status in asthma research. *Am J Respir Crit Care Med* 1994; 149: S31-39.

Rittenhouse BE. The relevance of search for effects under a clinical-trial lamppost: a key issue. *Med Decis Making* 1995; 15: 348-357.

Rittenhouse BE. Exorcising protocol-induced spirits: making the clinical trial relevant for economics. *Med Decis Making* 1997; 17: 331-339.

Rittenhouse BE, O'Brien BJ. Threats to the validity of pharmacoeconomic analyses based on clinical trial data. In: Spilker B (ed.) *Quality of Life and Pharmacoeconomics in Clinical Trials.* 2nd edn. Philadelphia: Lippincott-Raven, 1996: 1215-1223.

Roethlisberger FJ, Dickson WJ, Wright HA. *Management and the Worker: an account of a research program conducted by the Western Electric Company, Hawthorne Works, Chicago.* Cambridge: Harvard University Press, 1961.

Roos NP, Shapiro E, Tate R. Does a small minority of elderly account for a majority of health care expenditures? A sixteen-year perspective. *Milbank Quarterly* 1989; 67(3-4): 347-69.

Rosenzweig P, Brohier S, Zipfel A. Data on placebo in healthy volunteers : impact of experimental conditions on safety, and on laboratory and physiological variables during phase I trials. *Therapie* 1996; 51(4): 356-357.

Ross RN, Morris M, Sakowitz SR, Berman BA. Cost-effectiveness of including cromolyn sodium in the treatment program for asthma: a retrospective, records-based study. *Clin Ther* 1988; 10: 188-203.

Rubin DH, Bauman LJ, Lauby JL. The relationship between knowledge and reported behavior in childhood asthma. *J Dev Behav Pediatr* 1989; 10: 307-312.

Russell LB, Siegel JE, Daniels N, Gold MR, Luce BR, Mandelblatt JS. Cost-Effectiveness Analysis as a Guide to Resource Allocation in Health: Roles and Limitations. In: Gold MR, Seigel JE, Russell LB, Weinstein MC (eds) *Cost-effectiveness in Health and Medicine*. New York: Oxford University Press, 1996: 3-24.

Rothwell PM. Can overall results of clinical trials be applied to all patients? *Lancet* 1995; 345: 1616-1619.

Rutten van-Mölken MP, Custers F, van Doorslaer EK, Jansen CC, Heurman L, Maesen FP, Smeets JJ, Bommer AM, Raaijmakers JA. Comparison of

performance of four instruments in evaluating the effects of salmeterol on asthma quality of life. *Eur Resp J* 1995; 8: 888-898.

Rutten van-Mölken MP, van Doorslaer EK, Rutten FF. Economic appraisal of asthma and COPD care: a literature review 1980-1991. *Soc Sci Med* 1992; 35(2): 161-75.

Rutten-van Mölken MP, van Doorslaer EK, van Vliet RCJA. Statistical Analysis of cost outcomes in a randomized controlled clinical trial. In: *Costs and effects of pharmacotherapy in asthma and COPD.* Maastricht: Maastricht University, 1994: 170-189.

Rutten van-Mölken MP, Van Doorslaer EK, Jansen MC, Kerstjens HA, Rutten FF. Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1995; 151: 975-982.

Rutten van-Mölken MP, van Doorslaer EKA., Jansen MCC, Van Essen-Zandvliet EE, Rutten FFH. Cost-effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. *PharmacoEconomics* 1993; 4: 257-270.

Sansonetti M, Pretet S, Guioth P, Denormandie L, Marsac J. Évaluation du coût médical de l'asthme de l'adulte au cours d'une année de surveillance en milieu hospitalier. *Rev Mal Resp* 1989; 6: 169-75.

Schmier JK, Leddy NK. The complexity of treatment adherence in adults with asthma: challenges and opportunities. *J Asthma* 1998;35:455-472.

Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis* 1967; 20: 637-648.

Sculpher MJ, Buxton M. The episode-free day as a composite measure of effectiveness: an illustrative economic evaluation of formoterol versus salbutamol in asthma therapy. *PharmacoEconomics* 1993; 4: 345-352.

Sears MR. Descriptive epidemiology of asthma. *Lancet* 1997; 350(suppl II): 1-4.

Shwartz M, Iezzoni LI, Moskowitz MA, Ash AS, Sawitz E. The importance of comorbidities in explaining differences in patient costs. *Med Care* 1996; 34(8) : 767-782.

Simon G, Wagner E, Vonkorff M. Cost-effectiveness comparisons using 'real world' randomized trials: the case of new antidepressant drugs. *Jour Clin Epidemiol* 1995; 48: 363-373.

Sly RM. Changing asthma mortality. *Annals Allergy* 1994; 73(3): 259-68.

Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am Jour Resp Crit Care* Med 1997; 156: 787-793.

Soumerai SB, McLaughlin TJ, Ross-Degnan D, Casteris CS, Bollini P. Effects of limiting medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. *NEJM* 1994; 331(10): 650-5.

Soumerai SB, Ross-Degnan D, Fortess EE, Abelson J. A critical analysis of studies of state drug reimbursement policies: research in need of a discipline. *Milbank Quarterly* 1993; 71(2): 217-52.

Spilker B. *Guide to Clinical Trials* New York: Raven Press, 1991.

Statistics Canada. *E-STAT Education Resources 1996 Census of Population* Internet site 'http://estat.statcan.ca/cgi-win/ 1999.

Steiner JF, Koepsell TC, Fihn SD, Inui TS. A general method of compliance assessment using centralized pharmacy records. Description and validation. *Med Care* 1988; 26(8): 814-23.

Steinmetz KO, Volmer T, Trautmann M, Kielhorn A. Cost effectiveness of fluticasone and budesonide in patients with moderate asthma. *Clin Drug Invest* 1998; 16: 117-123.

Stempel DA, Durcannin-Robbins JF, Hedblom EC, Woolf R, Sturm LL, Stempel AB. Drug utilization evaluation identifies costs associated with high use of beta-adrenergic agonists. *Ann Allergy Asthma Immunol* 1996; 76: 153-158.

Stewart M. The validity of an interview to assess a patient's drug taking. *Amer Jour Prevent Med* 1987; 3(2): 95-100.

Sturdy P, Jaish J, Pereira F, Griffiths C, Dolan S, Toon P, Chambers M. Characteristics of general practices that prescribe appropriately for asthma. *BMJ* 1995; 311 : 1547-1548.

Suissa S, Dennis R, Ernst P, Sheehy O, Wood-Dauphinée S. Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma. *Ann of Int Med* 1997;126:177-183.

Sullivan SD. Cost-effectiveness of drug interventions. *Eur Resp Rev* 1996; 6: 116-118.

Sullivan S, Elixhauser A, Buist AS, Luce BR, Eisenberg J, Weiss KB. National Asthma Education and Prevention Program working group report on the cost effectiveness of asthma care. *Am J Resp Crit Care Med* 1996; 154: S84-95.

Sullivan SD, Weiss KB. Assessing cost-effectiveness in asthma care: building an economic model to study the impact of alternative intervention strategies. *Allergy* 1993; 48(17 Suppl): 146-152.

Summer W, Elson R, Tharpe L, Nelson S, Haponik EF. Aeorosol Bronchodilator Delivery Methods. *Arch Int Med* 1989; 149: 618-623.

Sumner B, Lurie N. Financial payment systems and asthma care. *Med Care* 1993; 31(3 Suppl): MS74-81.

Susser M. Editorial: The tribulations of trials--intervention in communities. *Amer J Public Health* 1995; 85(2): 156-158.

Swanborn PG. External validity abandoned. *Quality and Quantity* 1993; 27: 211-215.

Svenson LW, Woodhead SE, Platt GH. Estimation de la prévalence de l'asthme en Alberta: une étude fondée sur les dossiers du régime provincial d'assurance -maladie. *Mal Chron Canada* 1993; 14(31-6).

Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. *J Clin Epidemiol* 1995; 48: 999-1009.

Tarlo SM, Broder I, Davies GM, Leznoff A, Mintz S, Corey PN. Six-month double-blind, controll trial of high dose, concentrated beclomethasone dipropionate in the treatment of severe chronic asthma. *Chest* 1988; 93(5): 998-1002.

Taytard A. Assessing compliance in asthma patients. *Eur Resp Jour* 1992; 5(1): 125-126.

Taytard A, Touron D. Épidémiologie de l'asthme. *Rev Praticien (Paris)* 1992; 42: 2395-2397.

Thomas K, Peter JV, Cherian AM, Guyatt G. Cost-effectiveness of inhaled beta-agonists v. oral salbutamol in asthma: a randomized double-blind cross-over study. *Nat Med J India* 1996; 9: 159-162.

Tierce JC, Meller W, Berlow B, Gerth WC. Assessing the cost of albuterol inhalers in the Michigan and California Medicaid programs: a total cost-of-care approach. *Clin Ther* 1989; 11: 53-61.

Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993; 92(1): 64-77.

Torgerson DJ, Spencer A. Marginal costs and benefits. *BMJ* 1996; 312: 35-36.

Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ* 1986; 5: 1-30.

Torrance GW, Furlong W, Feeny D, Boyle M. Multi-Attribute Preference Functions Health Utilities Index. *PharmacoEconomics* 1995; 7: 503-520.

Torrance GW, Siegel JE, Luce BR. Framing and Designing the Cost-Effectiveness Analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC (eds) *Cost-Effectiveness in Health and Medicine*. Oxford: Oxford University Press, 1996: 54-81.

Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res* 1972; 7: 118-133.

Trautner C, Richter B, Berger M. Cost-effectiveness of a structured treatment and teaching programme on asthma. *Eur Resp Jour* 1993; 6(10): 1485-1491.

Turner MO, Gafni A, Swan D, FitzGerald JM. A review and economic evaluation of bronchodilator delivery methods in hospitalized patients. *Arch Int Med* 1996; 156: 2113-2118.

van Schayck CP, van Weel C, Folgering H, Verbeek AL, van Herwaarden CL. Treatment of patients with airflow obstruction by general practitioners and chest physicians. *Scand Journal Primary Health Care* 1989;**7**(3):137-142.

Venables TL, McConchie S, Follows RMA. A comparison of the cost-effectiveness of budesonide and fluticasone dry-powder devices in the management of adult asthma. *Brit J Med Econ* 1996; 10: 315-323.

Vollmer WM, O'Hollaren M, Ettinger KM, Stibolt T, Wilkins J, Buist S, Linton KLP, Osborne ML. Specialty differences in the management of asthma—a cross-sectional assessment of allergists' patients and generalists' patients in a large HMO. *Arch Intern Med* 1997; 157: 1201-1208.

Watt, J., F. Dixon, Thompson R, Burgess C, Crane J, Beasley R. The effect of the increased prescription charges on the collection of asthma drugs. *N Z Med Jour* 1992;105(932): 153-4.

Weiss KB, Budetti P. Examining issues in health care delivery for asthma. Background and workshop overview. *Med Care* 1993; 31(3 Suppl): MS9-19.

Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *NEJM* 1992; 326(13): 862-6.

Wilkins K. Personal communication of estimates of the age and gender specific prevalence of asthma from the Statistics Canada 1996-97 National Population Health Survey, 1999.

Wilkins K. Mao Y. Trends in rates of admission to hospital and death from asthma among children and young adults in Canada during the 1980s. *Can Med Assoc J* 1993; 148(2): 185-90.

Williams JI, Young W. Inventory of Studies on the Accuracy of Canadian Health Administrative Databases. Toronto: Institute for Clinical Evaluative Sciences, Pub. No 96-03-TR, December, 1996.

Wilson SR. Patient and physician behavior models related to asthma care. *Med Care* 1993; 31(3 Suppl): MS49-60.

Windsor RA, Bailey WC, Richards JM, Manzella B, Soong SJ, Brooks M. Evaluation of the efficacy and cost effectiveness of health education methods

to increase medication adherence among adults with asthma. *Amer J Public Health* 1990; 80(12): 1519-21.

Wissow LS, Gittelsohn Am, Szklo M, Starfield B, Mussman M. Poverty, race, and hospitalization for childhood asthma. *Amer J Public Health* 1988; 78(7): 777-82.

Woller W, Kruse J, Winter P, Mans EJ, Alberti L. Cortisone image and emotional support by key figures in patients with bronchial asthma. An empirical study. *Psychother Psychosom* 1993; 59(3-4): 190-6.

Wright RW, Larsen DF, Monie RG, Aldred RA. Benefits of a community-hospital pulmonary-rehabilitation program. *Resp Care* 1983; 28: 1474.

Yoon R, McKenzie DK, Miles DA, Bauman A. Characteristics of attenders and non-attenders at an asthma education programme. *Thorax* 1991; 46(12): 886-90.

Appendices

List of appendices

Appendix 1

Letters recruiting hospital subjects – French language

le 3 septembre 1996

Cher Monsieur, chère Madame:

Bonjour ! Vous vous souvenez de nous ? Vous avez déjà participé entre le_____et le _____à une étude portant sur un médicament contre l'asthme. Grâce à votre participation et à celle d'autres patients collaborateurs comme vous, tous les asthmatiques peuvent profiter d'une amélioration de traitement. Nous voulons vous remercier encore une fois d'avoir participé à cette étude. Nous vous contactons à nouveau parce que nous entreprenons une autre étude qui vise à savoir si le fait de participer à des études comme celle dans laquelle vous étiez inclus(e) peut affecter l'utilisation des soins de santé tels que les visites à l'hôpital, à la salle d'urgence, chez les médecins de famille, l'achat de médicaments, etc.

Nous aimerions donc solliciter votre participation, qui sera bien simple pour vous cette fois-ci. En effet, nous ne vous demandons pas de faire une visite à l'hôpital et **nous n'avons pas** besoin de faire une prise de sang . De fait, tout ce que nous vous demandons c'est **de nous indiquer votre consentement** sur la feuille ci-jointe.

Ce consentement nous autoriserait à consulter votre dossier contenant les informations de l'étude à laquelle vous avez participé, plus spécifiquement des renseignements sur les médications pour l'asthme et les autres traitements que vous avez reçus durant l'étude. Nous aimerions aussi obtenir des renseignements sur les médicaments contre l'asthme que vous avez pris, renseignements colligés dans le dossier de votre pharmacien. Tous ces renseignements resteront strictement confidentiels.

Le formulaire de consentement est inclus.

Si vous acceptez de participer à cette étude, nous vous prions de:

1.

Compléter *le formulaire de consentement ci-inclus, en mentionnant votre numéro d'assurance-maladie, les nom et adresse de votre pharmacie ou de vos pharmacies (une suggestion: si vous ne pouvez vous rappeler le nom et l'adresse de vos pharmacies, vous n'avez qu'à vérifier sur votre contenant de pilules ou sur la boîte contenant vos inhalateurs).*

2.

Signer *et inscrire en caractères majuscules votre nom et la date dans l'espace réservé au participant sur le formulaire de consentement, tout en trouvant un témoin de 18 ans ou plus qui apposera aussi son nom et la date en caractères majuscules, en plus de lui demander aussi de signer.*

3.

Retourner les deux copies dans l'enveloppe pré-estampillée ayant notre adresse ci-incluse. *Nous vous retournerons alors une de ces deux copies pour que vous la gardiez si vous le désirez.*

Si vous avez quelque question, n'hésitez pas à nous contacter en demandant à parler à Wendy Kennedy ou à Jean-Luc Malo à l'un ou l'autre des numéros suivants. Habituellement, quelqu'un vous répondra, mais si ceci n'était pas possible, nous avons un répondeur:

(514) 338-2669 ou

(514) 338-2796 (Hôpital du Sacré-Coeur)

Nous vous remercions beaucoup à l'avance pour votre aide et votre collaboration. Nous comptons sur votre participation pour pouvoir réaliser cette étude. Ces résultats sont essentiels pour comprendre l'effet qu'ont les essais cliniques de nouveaux médicaments sur l'utilisation des services de santé, ce qui devrait permettre une meilleure prise en charge des patients asthmatiques.

Veuillez recevoir l'expression de nos sentiments reconnaissants !

Jean-Luc Malo, M.D.

Wendy Kennedy

Merci beaucoup !

le 3 septembre 1996

Cher Monsieur, chère Madame:

Bonjour ! Vous vous souvenez d'un projet de recherche à l'Hôpital Laval ? Vous avez déjà participé entre le_____et le _____à une étude portant sur un médicament contre l'asthme. Grâce à votre participation et à celle d'autres patients collaborateurs comme vous, tous les asthmatiques peuvent profiter d'une amelioration de traitement. L'équipe de chercheurs veut vous remercier encore une fois d'avoir participé à cette étude. Une équipe de chercheurs de l'Université de Montréal vous contacte à nouveau parce que nous entreprenons une autre étude qui vise à savoir si le fait de participer à des études comme celle dans laquelle vous étiez inclus(e) peut affecter l'utilisation des soins de santé tels que les visites à l'hôpital, à la salle d'urgence, chez les médecins de famille, l'achat de médicaments, etc.

Nous aimerions donc solliciter votre participation, qui sera bien simple pour vous cette fois-ci. En effet, nous ne vous demandons pas de faire une visite à l'hôpital et **nous n'avons pas** besoin de faire une prise de sang . De fait, tout ce que nous vous demandons c'est **de nous indiquer votre consentement** sur la feuille ci-jointe.

Ce consentement nous autoriserait à consulter votre dossier contenant les informations de l'étude à laquelle vous avez participé, plus spécifiquement des renseignements sur les médications pour l'asthme et les autres traitements que vous avez reçus durant l'étude. Nous aimerions aussi obtenir des renseignements sur les médicaments contre l'asthme que vous avez pris, renseignements colligés dans le dossier de votre pharmacien. Tous ces renseignements resteront strictement confidentiels.

Le formulaire de consentement est inclus.

Si vous acceptez de participer à cette étude, nous vous prions de:

1. **Compléter** *le formulaire de consentement ci-inclus, en mentionnant votre numéro d'assurance-maladie, les nom et adresse de votre pharmacie ou de vos pharmacies (une suggestion: si vous ne pouvez vous rappeler le nom et l'adresse de vos pharmacies, vous n'avez qu'à vérifier sur votre contenant de pilules ou sur la boîte contenant vos inhalateurs).*

2. **Signer** *et inscrire en caractères majuscules votre nom et la date dans l'espace réservé au participant sur le formulaire de consentement, tout en trouvant un témoin de 18 ans ou plus qui apposera aussi son nom et la date en caractères majuscules, en plus de lui demander aussi de signer.*

3. **Retourner les deux copies dans l'enveloppe pré-estampillée ayant notre adresse ci-incluse.** *Nous vous retournerons alors une de ces deux copies pour que vous la gardiez si vous le désirez.*

Si vous avez quelque question, n'hésitez pas à nous contacter en demandant à parler à Joanne Milot (Québec) ou à Wendy Kennedy (Montréal) à l'un ou l'autre des numéros suivants. Habituellement, quelqu'un vous répondra, mais si ceci n'était pas possible, nous avons un répondeur:

(418) 656-8711 poste 5389 (Hôpital Laval) ou

(514) 338-2796 (Hôpital du Sacré-Coeur)

Nous vous remercions beaucoup à l'avance pour votre aide et votre collaboration. Nous comptons sur votre participation pour pouvoir réaliser cette étude. Ces résultats sont essentiels pour comprendre l'effet qu'ont les essais cliniques de nouveaux médicaments sur l'utilisation des services de santé, ce qui devrait permettre une meilleure prise en charge des patients asthmatiques.

Veuillez recevoir l'expression de nos sentiments reconnaissants !

Louis-Philippe Boulet, M.D. *Wendy Kennedy*

Merci beaucoup !

HÔPITAL GÉNÉRAL DE MONTRÉAL
THE MONTREAL GENERAL HOSPITAL

1650 avenue Cedar, suite D7.177
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Département de pneumologie
Respiratory Division

DR. P. ERNST
Directeur-Director

DR. N. COLMAN
DR. D. EIDELMAN
DR. S. GOTTFRIED

DR. J. GRUBER
DR. A. GURSAHANEY
DR. E. MATOUK
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Compléter *le formulaire de consentement ci-inclus, en mentionnant votre numéro d'assurance-maladie, les nom et adresse de votre pharmacie ou de vos pharmacies (une suggestion: si vous ne pouvez vous rappeler le nom et l'adresse de vos pharmacies, vous n'avez qu'à vérifier sur votre contenant de pilules ou sur la boîte contenant vos inhalateurs). S'il vous plaît, compléter une page 3 pour chaque pharmacie.*

2.

Signer *et inscrire en caractères majuscules votre nom et la date dans l'espace réservé au participant sur le formulaire de consentement, tout en trouvant un témoin de 18 ans ou plus qui apposera aussi son nom et la date en caractères majuscules, en plus de lui demander aussi de signer.*

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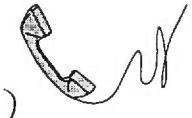
Si vous avez quelque question, n'hésitez pas à nous contacter en demandant à parler à à Wendy Kennedy (Montréal) à l'un ou l'autre des numéros suivants. Habituellement, quelqu'un vous répondra, mais si ceci n'était pas possible, nous avons un répondeur:

(514) 343-7365 (Université de Montréal) ou

(514) 338-2796 (Hôpital du Sacré-Coeur)



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Veuillez recevoir l'expression de nos sentiments reconnaissants !

[redacted]

Pierre-Paul Ernst, M.D.

[redacted]

Wendy Kennedy

Merci beaucoup !

Appendix 2

Letters recruiting hospital subjects – English language

September 3, 1996

Dear Mrs. Chose:

Hello again! Remember us? If you recall, you participated in a study from _____to _____ evaluating a treatment for your asthma. Because of your help and the help of other persons such as yourself, all asthmatics can benefit from improved treatment. We wish to thank you again for the help you gave us, and are writing to you because of that help. We are starting a new study which looks at how participating in that and similar studies affect the use of health services such as medications, hospital stays, emergency room visits and doctors' appointments. This study examines the files which contain the records of this use of health services in the past.

We would greatly appreciate your participation. Don't worry, your role in this study is very simple. We're **not** asking you to make a trip to the hospital, we **don't need** (surprise!) any more of your blood. All we are asking you to do is **indicate your consent** to consult the files by signing the enclosed forms and giving us some information.

If you give your consent, the hospital files which contain the information about the study in which you participated will be consulted, and a few details of the asthma medications which you took and the other treatments for your asthma which you received during the course of the study will be collected. Afterwards, we will contact your pharmacist(s) to collect additional information with respect to the medications you received to treat your asthma. All this information will be kept strictly confidential. You will find more details in the attached consent form.

If you agree to participate in this study please:

1.

Complete *the attached consent form, with your health insurance number (on the Quebec Health Card) and the name and address of the pharmacy or pharmacies where you buy your asthma medications. (Hint: If you cannot remember the name or address, you can find it on the label of your prescription medication bottles or inhaler pumps).*

2.

Sign, *and print your name and the date in the space for "Participant" on the consent form on both copies of the form, arranging for someone over the age of 18 to be able to witness the signature and sign as a witness. This person also must sign, and print his or her name and the date in the space for "Witness".*

3.

Return *the two copies in the enclosed stamped self-addressed envelope. We will then promptly return one of the consent forms completed by a member of the research group for your records.*

If you have any questions, do not hesitate to call either Wendy Kennedy or Dr.. Jean-Luc Malo, at either of the following numbers. Normally someone will respond in person during business hours, but we have an answering machine in case this is not possible:

(514) 338-2669 or

(514) 338-2796 (Sacré-Coeur Hospital)

Thank you very much for your time and your assistance. We are counting on your participation to allow us to realise the study. The results are essential to our understanding the effect of new asthma drug treatments on the delivery of health services, and to help bring better overall care for persons with asthma.

Yours sincerely

Jean-Luc Malo, M.D.

Wendy Kennedy

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If you have any questions, do not hesitate to call Wendy Kennedy at either of the following numbers. Normally someone will respond in person during business hours, but we have an answering machine in case this is not possible:

(514) 343- 7365 (University of Montreal) or

([redacted]

Thank you very much for your time and your assistance. We are counting on your participation to allow us to realise the study. The results are essential to our understanding the effect of new asthma drug treatments on the delivery of health services, and to help bring better overall care for persons with asthma.

Yours sincerely

Pierre-Paul Ernst, M.D. *Wendy Kennedy*

Appendix 3

Clinical trial subjects consent forms – French language

HOPITAL DU SACRé-COEUR -- UNIVERSITé DE MONTRéAL

Formulaire d'information (centre)

Coût-efficacité "pratique" par comparaison avec coût-efficacité : l'ordre de l'essai clinique des corticosteroïdes inhalés dans le traitement de l'asthme

Nom du chercheur Un projet de recherche examinant l'utilisation des soins de santé par des asthmatiques québécois prenant des stéroïdes en inhalation est en cours sous la responsabilité d'un groupe de chercheurs de l'Université de Montréal, dirigé par le Dr. André-Pierre Contandriopoulos, économiste de la santé, Dr. Claudine Laurier, pharmacienne, Dr. Jean-Luc Malo, pneumologue, ainsi que d'une étudiante au doctorat, Wendy Kennedy. Cette étude a été approuvée par le Comité d'Éthique de l'hôpital du Sacré-Coeur de Montréal.

But de l'étude Cette étude s'intéresse à l'utilisation des soins de santé dans deux groupes de sujets asthmatiques: ceux de la population générale et ceux qui participent à des essais cliniques. Les indices décrivant l'utilisation des soins de santé sont les hospitalisations, les visites dans les salles d'urgence, les visites aux médecins et les ordonnances de médicaments antiasthmatiques. Les autres médicaments ne seront pas considérés dans l'analyse, sauf pour estimer le presence des autres problèmes de santé.

Procédures de l'étude Si vous acceptez de participer à cette étude, votre implication consistera à identifier vos pharmacies habituelles et à consentir que le groupe de recherche ait accès à l'information de vos dossiers des pharmacies et aux dossiers hospitaliers relatifs à votre participation à des essais cliniques. Ensuite, certaines informations aux dossiers du gouvernement du Québec qui contiennent les renseignements relatifs à votre utilisation de soins de santé au cours de deux années vont être jumelées. Les renseignements obtenus sont limités à une période de deux ans qui se situera entre le 1er janvier 1988 et le 31 décembre 1996. Pour faciliter cette demande, nous vous demandons de nous fournir votre numéro d'assurance-maladie et les noms des pharmaciens où vous vous procurez vos médicaments. Votre numéro ne nous servira qu'à des fins d'études et aucun jugement ne sera porté sur votre utilisation de services.

Risques potentiels Il n'y a en soi aucun risque potentiel associé à cette étude car elle n'implique aucune modification au traitement que vous recevez. Le seul inconvénient, s'il en est, sera de consacrer environ 10 minutes au total pour lire ce formulaire et pour donner l'information.

Bienfaits potentiels Il n'y a pas de bénéfice personnel relatif à cette étude. Par contre, la réalisation de cette étude permettra de mieux connaître l'impact que les problèmes de santé comme l'asthme ont sur le système de santé.

Confidentialité de dossiers Certaines informations sur l'utilisation des services de soins de santé et médicaments pour traiter l'asthme seront puisées de votre dossier hospitalier, et de votre dossier de médicaments détenu à votre (vos) pharmacie(s). Tous les renseignements recueillis à votre sujet au cours de l'étude demeureront strictement confidentiels et vous ne serez identifié(e) que par vos initiales et un numéro de code afin de préserver l'anonymat. Toute l'information puisée de votre dossier médical détenu au Ministère de la Santé et des Service Sociaux le sera d'une façon anonyme avec un numéro de code brouillé afin de préserver l'anonymat. Aucune publication résultant de cette étude ne renfermera quoi que ce soit qui puisse permettre de vous identifier. Les informations que nous allons recueillir ne seront utilisées que pour la présente étude. Cependant, votre dossier pourra être consulté par des représentants de l'organisme ou de l'entreprise impliquée et des organismes gouvernementaux de santé autorisés. Tous ces organismes adhèrent à une politique de stricte confidentialité.

Indemnisation En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, les organismes, les entreprises ou les institutions impliqués de leurs responsabilités légales et professionnelles.

Droit d'abandonner l'étude Votre participation est entièrement volontaire. Vous êtres libre de refuser d'y participer. Vous pouvez également vous retirer de l'étude à n'importe quel moment en faisant connaître votre décision au chercheur ou à l'un de ses assistants. Votre refus de participer ou de vous y soustraire à n'importe quel moment n'entraînera pour vous aucune conséquence défavorable sur les soins qui vous seront fournis par la suite. Le chercheur reponsable de l'étude peut aussi décider de vous retirer de l'étude sans votre consentement.

Personnes à contacter Si vous avez des questions à poser au sujet de cette étude ou s'il survient un incident quelconqueou si vous désirez vous retirer de l'étude, vous pouvez contacter en tout temps:

Wendy Kennedy, assistante de recherche, téléphone: 514 343-7365 ou [redacted]

Consentement du sujet

La nature de l'étude, les procédés, les risques et les bénéfices que comporte ma participation à cette étude ainsi que le caractère confidentiel des informations qui seront recueillies au cours de l'étude m'ont été expliqués.

J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et de recevoir des réponses qui m'ont satisfait(e).

Je, soussigné(e), accepte volontairement de participer à cette étude. Je peux me retirer en tout temps sans que cela ne nuise aux relations avec mon médecin, mon pharmacien, et les autre intervenants et ce, sans préjudice d'aucune sorte.

Je reconnais avoir reçu une copie signée de ce formulaire d'information et de consentement.

Je donne l'autorisation:

1. au(x) pharmacien(s) dont le(s) nom(s) apparait(apparaissent) sur ce formulaire, de fournir les détails des ordonnances que l'on m'a livrées pour traiter mon asthme,

2. à l'hôpital, de fournir les détails de ma médication, des traitements et des tests que j'ai passés au cours de l'essai clinique auquel j'ai participé,

à Wendy Kennedy ou Claudine Laurier. Ces renseignements porteront sur une période consécutive de 24 mois à partir du_____ jusqu'au _____, inclusivement.

Mon numéro **d'assurance-maladie** (sur la carte soleil) est:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Mes pharmacies sont: (vous pouvez regarder sur vos bouteilles de médicaments)

_____	_____
nom	adresse
_____	_____
nom	adresse
_____	_____
nom	adresse

Cette autorisation est valable pour un période de 90 jours à compter de la date de la signature de ce document.

Participant

Nom:_____ Prénom: _____

Signature: _____ Date: _____/_____/_____

Parent ou tuteur (si moins de 18 ans)

Je consens à ce que _____ participe au projet de recherche et j'atteste qu'il ne s'y oppose pas.

Nom:_____ Prénom: _____

En ma qualité de _____

Signature: _____ Date: _____/_____/_____

Témoin

Nom:_____ Prénom: _____

Signature: _____ Date: _____/_____/_____

Réservé pour le responsable de l'étude:

Je, _____, certifie avoir expliqué à la personne ci-haut mentionnée la nature et les risques de la participation à cette étude, et que la personne a l'opportunité de ce retirer de l'étude en tout temps. Je l'ai assurée que sa participation sera tenue confidentielle.

Responsable de l'étude:

Nom:_____ Prénom: _____

Signature: _____ Date: _____/_____/_____

PROJET HOPITAL LAVAL ET UNIVERSITÉ DE MONTRÉAL

Formulaire d'information (centre)

Coût-efficacité "pratique" par comparaison avec coût-efficacité : l'ordre de l'essai clinique des corticosteroïdes inhalés dans le traitement de l'asthme

Nom du chercheur Un projet de recherche examinant l'utilisation des soins de santé par des asthmatiques québécois prenant des stéroïdes en inhalation est en cours sous la responsabilité d'un groupe de chercheurs de l'Université de Montréal, dirigé par le Dr. André-Pierre Contandriopoulos, économiste de la santé, Dr. Claudine Laurier, pharmacienne, Dr. Jean-Luc Malo, pneumologue, ainsi que d'une étudiante au doctorat, Wendy Kennedy. Cette étude a été approuvée par le Comité d'Éthique de l'hôpital Laval.

But de l'étude Cette étude s'intéresse à l'utilisation des soins de santé dans deux groupes de sujets asthmatiques: ceux de la population générale et ceux qui participent à des essais cliniques. Les indices décrivant l'utilisation des soins de santé sont les hospitalisations, les visites dans les salles d'urgence, les visites aux médecins et les ordonnances de médicaments antiasthmatiques. Les autres médicaments ne seront pas considérés dans l'analyse, sauf pour estimer le presence des autres problèmes de santé.

Procédures de l'étude Si vous acceptez de participer à cette étude, votre implication consistera à identifier vos pharmacies habituelles et à consentir que le groupe de recherche ait accès à l'information de vos dossiers des pharmacies et aux dossiers hospitaliers relatifs à votre participation à des essais cliniques. Ensuite, certaines informations aux dossiers du gouvernement du Québec qui contiennent les renseignements relatifs à votre utilisation de soins de santé au cours de deux années vont être jumelées. Les renseignements obtenus sont limités à une période de deux ans qui se situera entre le 1er janvier 1988 et le 31 décembre 1995. Pour faciliter cette demande, nous vous demandons de nous fournir votre numéro d'assurance-maladie et les noms des pharmaciens où vous vous procurez vos médicaments. Votre numéro ne nous servira qu'à des fins d'études et aucun jugement ne sera porté sur votre utilisation de services.

Risques potentiels Il n'y a en soi aucun risque potentiel associé à cette étude car elle n'implique aucune modification au traitement que vous recevez. Le seul inconvénient, s'il en est, sera de consacrer environ 10 minutes au total pour lire ce formulaire et pour donner l'information.

Bienfaits potentiels Il n'y a pas de bénéfice personnel relatif à cette étude. Par contre, la réalisation de cette étude permettra de mieux connaître l'impact que les problèmes de santé comme l'asthme ont sur le système de santé.

Confidentialité de dossiers Certaines informations sur l'utilisation des services de soins de santé et médicaments pour traiter l'asthme seront puisées de votre dossier hospitalier, et de votre dossier de médicaments détenu à votre (vos) pharmacie(s). Tous les renseignements recueillis à votre sujet au cours de l'étude demeureront strictement confidentiels et vous ne serez identifié(e) que par vos initiales et un numéro de code afin de préserver l'anonymat. Toute l'information puisée de votre dossier médical détenu au Ministère de la Santé et des Service Sociaux le sera d'une façon anonyme avec un numéro de code brouillé afin de préserver l'anonymat. Aucune publication résultant de cette étude ne renfermera quoi que ce soit qui puisse permettre de vous identifier. Les informations que nous allons recueillir ne seront utilisées que pour la présente étude. Cependant, votre dossier pourra être consulté par des représentants de l'organisme ou de l'entreprise impliquée et des organismes gouvernementaux de santé autorisés. Tous ces organismes adhèrent à une politique de stricte confidentialité.

Indemnisation En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, les organismes, les entreprises ou les institutions impliqués de leurs responsabilités légales et professionnelles.

Droit d'abandonner l'étude Votre participation est entièrement volontaire. Vous êtres libre de refuser d'y participer. Vous pouvez également vous retirer de l'étude à n'importe quel moment en faisant connaître votre décision au chercheur ou à l'un de ses assistants. Votre refus de participer ou de vous y soustraire à n'importe quel moment n'entraînera pour vous aucune conséquence défavorable sur les soins qui vous seront fournis par la suite. Le chercheur reponsable de l'étude peut aussi décider de vous retirer de l'étude sans votre consentement.

Personnes à contacter Si vous avez des questions à poser au sujet de cette étude ou s'il survient un incident quelconqueou si vous désirez vous retirer de l'étude, vous pouvez contacter en tout temps:

Wendy Kennedy, assistante de recherche, téléphone: 514 343-7365 ou [redacted]

Consentement du sujet

La nature de l'étude, les procédés, les risques et les bénéfices que comporte ma participation à cette étude ainsi que le caractère confidentiel des informations qui seront recueillies au cours de l'étude m'ont été expliqués.

J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et de recevoir des réponses qui m'ont satisfait(e).

Je, soussigné(e), accepte volontairement de participer à cette étude. Je peux me retirer en tout temps sans que cela ne nuise aux relations avec mon médecin, mon pharmacien, et les autre intervenants et ce, sans préjudice d'aucune sorte.

Je reconnais avoir reçu une copie signée de ce formulaire d'information et de consentement.

Je donne l'autorisation:

1. au(x) pharmacien(s) dont le(s) nom(s) apparait(apparaissent) sur ce formulaire, de fournir les détails des ordonnances que l'on m'a livrées pour traiter mon asthme,

2. à l'hôpital, de fournir les détails de ma médication, des traitements et des tests que j'ai passés au cours de l'essai clinique auquel j'ai participé,

à Wendy Kennedy ou Claudine Laurier. Ces renseignements porteront sur une période consécutive de 24 mois à partir du _____ jusqu'au _____, inclusivement.

Mon numéro **d'assurance-maladie** (sur la carte soleil) est:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Mes pharmacies sont: (vous pouvez regarder sur vos bouteilles de médicaments)

_____	_____
nom	adresse
_____	_____
nom	adresse
_____	_____
nom	adresse

Cette autorisation est valable pour un période de 90 jours à compter de la date de la signature de ce document.

Participant

Nom:_____ Prénom: _____

Signature: _____ Date: ____/_____/_____

Parent ou tuteur (si moins de 18 ans)

Je consens à ce que _____ participe au projet de recherche et j'atteste qu'il ne s'y oppose pas.

Nom:_____ Prénom: _____

En ma qualité de _____

Signature: _____ Date: ____/_____/_____

Témoin

Nom:_____ Prénom: _____

Signature: _____ Date: ____/_____/_____

Réservé pour le responsable de l'étude:

Je, _____, certifie avoir expliqué à la personne ci-haut mentionnée la nature et les risques de la participation à cette étude, et que la personne a l'opportunité de se retirer de l'étude en tout temps. Je l'ai assurée que sa participation sera tenue confidentielle.

Responsable de l'étude:

Nom:_____ Prénom: _____

Signature: _____ Date: ____/_____/_____

HÔPITAL GÉNÉRAL DE MONTRÉAL
THE MONTREAL GENERAL HOSPITAL

1650 avenue Cedar, suite D7.177
Montréal, Québec H3G 1A4
Tel.: (514) 934-8014 Fax: (514) 934-8226

Département de pneumologie
Respiratory Division

DR. P. ERNST
Directeur-Director

DR. N. COLMAN
DR. D. EIDELMAN
DR. S. GOTTFRIED

DR. J. GRUBER
DR. A. GURSAHANEY
DR. E. MATOUK
DR. A. ZIDULKA

PROJET HOPITAL GÉNÉRAL DE MONTRÉAL ET UNIVERSITÉ DE MONTRÉAL
Formulaire d'information (centre)

Coût-efficacité "pratique" par comparaison avec coût-efficacité : l'ordre de l'essai clinique des corticostéroïdes inhalés dans le traitement de l'asthme

Nom du chercheur Un projet de recherche examinant l'utilisation des soins de santé par des asthmatiques québécois prenant des stéroïdes en inhalation est en cours sous la responsabilité d'un groupe de chercheurs de l'Université de Montréal, dirigé par le Dr. André-Pierre Contandriopoulos, économiste de la santé, Dr. Claudine Laurier, pharmacienne, Dr. Jean-Luc Malo, pneumologue, ainsi que d'une étudiante au doctorat, Wendy Kennedy. Cette étude a été approuvée par le Comité d'Éthique de l'hôpital Général de Montréal.

But de l'étude Cette étude s'intéresse à l'utilisation des soins de santé dans deux groupes de sujets asthmatiques: ceux de la population générale et ceux qui participent à des essais cliniques. Les indices décrivant l'utilisation des soins de santé sont les hospitalisations, les visites dans les salles d'urgence, les visites aux médecins et les ordonnances de médicaments antiasthmatiques. Les autres médicaments ne seront pas considérés dans l'analyse, sauf pour estimer le présence des autres problèmes de santé.

Procédures de l'étude Si vous acceptez de participer à cette étude, votre implication consistera à identifier vos pharmacies habituelles et à consentir que le groupe de recherche ait accès à l'information de vos dossiers des pharmacies et aux dossiers hospitaliers relatifs à votre participation à des essais cliniques. Ensuite, certaines informations aux dossiers de la Régie d'Assurance Maladie du Québec et Med-Echo qui contiennent les renseignements relatifs à votre utilisation de soins de santé (par exemple les visites médicales et les séjours hospitaliers) au cours de deux années vont être jumelées. Les renseignements obtenus sont limités à une période de deux ans qui se situera entre le 1er janvier 1988 et le 31 décembre 1996. Pour faciliter cette demande, nous vous demandons de nous fournir votre numéro d'assurance-maladie et les noms des pharmacies où vous vous procurez vos médicaments. Votre numéro ne nous servira qu'à des fins d'études et aucun jugement ne sera porté sur votre utilisation de services.

Risques potentiels Il n'y a en soi aucun risque potentiel associé à cette étude car elle n'implique aucune modification au traitement que vous recevez. Le seul inconvénient, s'il en est, sera de consacrer environ 10 minutes au total pour lire ce formulaire et pour donner l'information.

Bienfaits potentiels Il n'y a pas de bénéfice personnel relatif à cette étude. Par contre, la réalisation de cette étude permettra de mieux connaître l'impact que les problèmes de santé comme l'asthme ont sur le système de santé.

Confidentialité de dossiers Certaines informations sur l'utilisation des services de soins de santé et médicaments pour traiter l'asthme seront puisées de votre dossier hospitalier, et de votre dossier de médicaments détenu à votre (vos) pharmacie(s). Tous les renseignements recueillis à votre sujet au cours de l'étude demeureront strictement confidentiels et vous ne serez identifié(e) que par vos initiales et un numéro de code afin de préserver l'anonymat. Toute l'information puisée de votre dossier médical détenu au Ministère de la Santé et des Service Sociaux le sera d'une façon anonyme avec un numéro de code brouillé afin de préserver l'anonymat. Aucune publication résultant de cette étude ne renfermera quoi que ce soit qui puisse permettre de vous identifier. Les informations que nous allons recueillir ne seront utilisées que pour la présente étude. Cependant, votre dossier pourra être consulté par des représentants de l'organisme ou de l'entreprise impliquée et des organismes gouvernementaux de santé autorisés. Deux comités, le Comité des essais cliniques et le Comité d'éthique de recherche de L'Hôpital Général de Montréal peuvent revoir les dossiers de recherche afin d'assurer la conformité avec les réglementations de recherche sur les êtres humains. Tous ces organismes adhèrent à une politique de stricte confidentialité.

Indemnisation En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, les organismes, les entreprises ou les institutions impliqués de leurs responsabilités légales et professionnelles.

Droit d'abandonner l'étude Votre participation est entièrement volontaire. Vous êtres libre de refuser d'y participer. Vous pouvez également vous retirer de l'étude à n'importe quel moment en faisant connaître votre décision au chercheur ou à l'un de ses assistants. Votre refus de participer ou de vous y soustraire à n'importe quel moment n'entraînera pour vous aucune conséquence défavorable sur les soins qui vous seront fournis par la suite. Le chercheur responsable de l'étude peut aussi décider de vous retirer de l'étude sans votre consentement.

Personnes à contacter Si vous avez des questions à poser au sujet de cette étude ou s'il survient un incident quelconque, ou si vous désirez vous retirer de l'étude, vous pouvez contacter en tout temps:

Wendy Kennedy, assistante de recherche, téléphone: 514 343-7365 ou [redacted]

Et si vous avez des questions concernant le protocole de recherche vouz pouvez contacter:

M. Glenn Fash, représentant des patients, téléphone: [redacted]

Consentement du sujet

La nature de l'étude, les procédés, les risques et les bénéfices que comporte ma participation à cette étude ainsi que le caractère confidentiel des informations qui seront recueillies au cours de l'étude m'ont été expliqués.

J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et de recevoir des réponses qui m'ont satisfait(e).

Je, soussigné(e), accepte volontairement de participer à cette étude. Je peux me retirer en tout temps sans que cela ne nuise aux relations avec mon médecin, mon pharmacien, et les autre intervenants et ce, sans préjudice d'aucune sorte. Je reconnais avoir reçu une copie signée de ce formulaire d'information et de consentement.

Je donne l'autorisation:

1. au(x) pharmacien(s) dont le(s) nom(s) apparaît(apparaissent) sur ce formulaire, de fournir les détails des ordonnances que l'on m'a livrées pour traiter mon asthme,

2. à l'hôpital, de fournir les détails de la médication que j'ai reçue, le type et le nombre de traitements et de tests que j'ai passés au cours de l'essai clinique auquel j'ai participé, (par exemple, les doses et dates des médicaments anti-asthmatiques fournis, le nombre et type des tests de fonction respiratoire, des échantillons de sang et d'urine, le nombre d'examens physiques),

à Wendy Kennedy ou Claudine Laurier. Ces renseignements porteront sur une période consécutive de 24 mois à partir du_____ jusqu'au _____, inclusivement.

Mon numéro **d'assurance-maladie** (sur la carte soleil) est:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Mon numéro d'assurance-maladie sera utilisé pour obtenir de l'information de la Régie d'Assurance Maladie du Québec et Med-Echo. Toute information sera regroupé et personne sera identifée individuellement.

Mon pharmacie est: (vous pouvez regarder sur vos bouteilles de médicaments)

_____ _____

nom adresse

(Complétez une page par pharmacie.) Cette autorisation est valable pour un période de 90 jours à compter de la date de la signature de ce document.

Participant

Nom:_____ Prénom: _____

Signature: _____ Date: _____/_____/_____

Parent ou tuteur (si moins de 18 ans)

Je consens à ce que _____ participe au projet de recherche et j'atteste qu'il ne s'y oppose pas.

Nom:_____ Prénom: _____

En ma qualité de _____

Signature: _____ Date: _____/_____/_____

Témoin

Nom:_____ Prénom: _____

Signature: _____ Date: _____/_____/_____

Réservé pour le responsable de l'étude:

Je, _____, certifie avoir expliqué à la personne ci-haut mentionnée la nature et les risques de la participation à cette étude, et que la personne a l'opportunité de se retirer de l'étude en tout temps. Je l'ai assurée que sa participation sera tenue confidentielle.

Responsable de l'étude:

Nom:_____ Prénom: _____

Signature: _____ Date: _____/_____/_____

Appendix 4

Clinical trial subjects consent forms – English language

SACRÉ-COEUR HOSPITAL-- UNIVERSITY OF MONTRÉAL

Information Form (centre)

Cost-efficacy vs, cost-effectiveness: inhaled corticosteroids in the treatment of asthma

Researchers' names A research project looking at the use of health services by asthmatics in Quebec taking inhaled corticosteroids is underway directed by a group of researchers at the University of Montreal. The group consists of Dr. André-Pierre Contandriopoulos, Health Economist, Dr. Claudine Laurier, Pharmacist, Dr. Jean-Luc Malo, Pneumologist, as well as a doctoral student, Wendy Kennedy. The study has been approved by the Ethics Committee of Montreal Sacré-Coeur Hospital.

Study objective The study explores the use of health services by two groups of asthmatics, those in the general population and those who have participated in clinical studies. The use of health services consists of hospital stays, emergency room visits, physician visits, and prescription drugs to treat asthma. Other drugs are not included in the study, except to estimate the presence of other health problems.

Study procedures If you agree to participate in this study, your involvement consists of identifying the pharmacies which you normally use and granting permission to the research group to have access to your pharmacy file and the hospital file dealing with the clinical study in which you participated. Afterwards, certain information from the Quebec Health program files which contain the data about your health services utilisation will be added. The information collected will be limited to a period of two years somewhere between January 1988 and December 1995. To allow us access to this information, we need your health insurance number and the name(s) of the pharmacy(ies) where you purchase your medications. Your health insurance number will be used only for this study, and no judgement will be made of the health services used.

Potential risk There is no risk associated with participating in this study, because it does not imply any change or modification in the treatment you receive. The only inconvenience, if there is any, is to spend a total of approximately 10 minutes reading this form and completing the information requested.

Potential benefit There is no personal benefit associated with your participation in this study. On the other hand, the study will allow a greater understanding of the impact of health problems such as asthma on the health care system.

Confidentiality of the information Information about the use of health services and medications for the treatment of asthma will be extracted from your hospital file and from your pharmacy drug file. All the information extracted will remain strictly confidential and you will be identified only by a code number and initials in order to assure anonymity. In none of the publications resulting from the study will you be identifiable in any way. The information extracted will be used only for the purposes of this study. On the other hand, your data files could be consulted by representatives of participating organisations or authorised government health organisations. All of these organisations adhere to policies of strict confidentiality.

Indemnity By agreeing to participate in this study, you are not giving up any of your rights, nor are you releasing the researchers, the organisations involved, the groups or institutions from their legal or professional responsibilities.

Right to abandon study Your participation is entirely voluntary. You are free to refuse to participate. You can as well withdraw from the study at any time by making your decision known to any one of the researchers or their assistants. Your refusal to participate or your decision at any time to withdraw will have no unfavorable effect on the health care you receive subsequently. The researcher responsible for the study can also decide to withdraw you at any time from the study without your consent.

Persons to contact If you have any questions to ask about the study, or if anything arises or if you wish to withdraw from the study, you can contact at any time:

Wendy Kennedy, research assistant, telephone: 514 343-7365 or [redacted]

Subject's consent

The nature of the study, the procedures, the risks and the benefits which result from my participation in this study, as well as the confidential nature of the information gathered over the course of the study have been explained to me.

I have had the opportunity to ask questions about all aspects of the study and have received satisfactory responses.

I, the undersigned, accept voluntarily to participate in this study. I can withdraw at any time and it will not affect the relationship with my physician, my pharmacist or any of the other intervenants, and results in no prejudice of any kind.

I acknowledge receipt of a signed copy of this information form and consent.

I authorise:

1. the pharmacy(ies) whose name(s) appear(s) on this form to supply details of the prescriptions which I have received to treat my asthma,

2. the hospital, to supply details of the medication I received, and treatments tests I received during the course of the clinical study in which I participated,

to Wendy Kennedy or Claudine Laurier. The information released covers a period of 24 consecutive months from _____ to _____, inclusive.

My Health Insurance Number (on the "carte soleil") is:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

My pharmacies are: (Look on your prescription bottle labels)

_____	_____
name	address
_____	_____
name	address
_____	_____
name	address

This authorisation is valid for a period of 90 days from the date of the signature on the document.

Participant

Surname:_____ First name: _____

Signature: _____ Date: _____/_____/_____

Parent or guardian (if less than 18 years old)

I give my consent to _____ to participate in the research project and I attest that he/she is not unwilling.

Surname:_____ First name: _____

In my capacity as _____

Signature: _____ Date: _____/_____/_____

Witness

Surname:_____ First name: _____

Signature: _____ Date: _____/_____/_____

Reserved for the study group:

I, _____, certify to having explained to the above participant the nature of the risks associated with participation in this study, and that that person has the right to withdraw at any time. I also gave the assurance that participation would be kept confidential.

Responsable for study:

Surname:_____ First name:_____

Signature: _____ Date: _____/_____/_____

HÔPITAL GÉNÉRAL DE MONTRÉAL
THE MONTREAL GENERAL HOSPITAL

1650 avenue Cedar, suite D7.177
Montréal, Québec H3G 1A4
Tel.: (514) 934-8014 Fax: (514) 934-8226

Département de pneumologie
Respiratory Division

DR. P. ERNST
Directeur-Director

DR. N. COLMAN
DR. D. EIDELMAN
DR. S. GOTTFRIED

DR. J. GRUBER
DR. A. GURSAHANEY
DR. E. MATOUK
DR. A. ZIDULKA

Project: MONTREAL GENERAL HOSPITAL & UNIVERSITY OF MONTRÉAL
Information Form (centre)

Cost-efficacy vs. cost-effectiveness: inhaled corticosteroids in the treatment of asthma

Researchers' names A research project looking at the use of health services by asthmatics in Quebec taking inhaled corticosteroids is underway directed by a group of researchers at the University of Montreal. The group consists of Dr. André-Pierre Contandriopoulos, Health Economist, Dr. Claudine Laurier, Pharmacist, Dr. Jean-Luc Malo, Pneumologist, as well as a doctoral student, Wendy Kennedy. The study has been approved by the Ethics Committee of Montreal General Hospital.

Study objective The study explores the use of health services by two groups of asthmatics, those in the general population and those who have participated in clinical studies. The use of health services consists of hospital stays, emergency room visits, physician visits, and prescription drugs to treat asthma. Other drugs are not included in the study, except to estimate the presence of other health problems.

Study procedures If you agree to participate in this study, your involvement consists of identifying the pharmacies which you normally use and granting permission to the research group to have access to your pharmacy file and the hospital file dealing with the clinical study in which you participated. Afterwards, certain information from the Quebec Health program files which contain the data about your health services utilization, such as physician visits and hospital stays, will be added. The information collected will be limited to a period of two years somewhere between January 1988 and December 1996. To allow us access to this information, we need your health insurance number and the name(s) of the pharmacy(ies) where you purchase your medications. Your health insurance number will be used only for this study, and no judgment will be made of the health services used.

Potential risk There is no risk associated with participating in this study, because it does not imply any change or modification in the treatment you receive. The only inconvenience, if there is any, is to spend a total of approximately 10 minutes reading this form and completing the information requested.

Confidentiality of the information Information about the use of health services and medications for the treatment of asthma will be extracted from your hospital file and from your pharmacy drug file. All the information extracted will remain strictly confidential and you will be identified only by a code number and initials in order to assure anonymity. In none of the publications resulting from the study will you be identifiable in any way. The information extracted will be used only for the purposes of this study. On the other hand, your data files could be consulted by representatives of participating organizations or authorized government health organizations. The hospital Research Ethics and Clinical Trials Committees may review the research records to monitor compliance with Institutional regulations regarding research involving human subjects. All of these organizations adhere to policies of strict confidentiality.

Indemnity By agreeing to participate in this study, you are not giving up any of your rights, nor are you releasing the researchers, the organizations involved, the groups or institutions from their legal or professional responsibilities.

Right to abandon study Your participation is entirely voluntary. You are free to refuse to participate. You can as well withdraw from the study at any time by making your decision known to any one of the researchers or their assistants. Your refusal to participate or your decision at any time to withdraw will have no unfavorable effect on the health care you receive subsequently. The researcher responsible for the study can also decide to withdraw you at any time from the study without your consent.

Persons to contact If you have any questions to ask about the study, or if anything arises or if you wish to withdraw from the study, you can contact at any time:

Wendy Kennedy, research assistant, telephone: 514 343-7365 or [redacted]

Additionally, if there are questions related to the study protocol the following patient representative may be contacted at the Montreal General Hospital:

Mr. Glenn Fash, telephone [redacted]

Participant's consent

The nature of the study, the procedures, the risks and the benefits which result from my participation in this study, as well as the confidential nature of the information gathered over the course of the study have been explained to me.

I have had the opportunity to ask questions about all aspects of the study and have received satisfactory responses.

I, the undersigned, accept voluntarily to participate in this study. I can withdraw at any time and it will not affect the relationship with my physician, my pharmacist or any of the other intervenants, and results in no prejudice of any kind. I acknowledge receipt of a signed copy of this information form and consent.

I authorize:

1. the pharmacy(ies) whose name(s) appear(s) on this form to supply details of the prescriptions which I have received to treat my asthma,

2. the hospital, to supply details of the medication I received, and the type and number of treatments and tests I received which were administered as part of the research procedures of the clinical study in which I participated (for example, the doses and dates of anti-asthma medication delivered, the number and type of respiratory function tests, blood and urine sample tests, number of physical exams),

to Wendy Kennedy or Claudine Laurier. The information released covers a period of 24 consecutive months from _____ to _____, inclusive.

My Health Insurance Number (on the "carte soleil") is:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

My health insurance number will be used to obtain information the Quebec Health program files. All information will be gathered on a group basis and no person will be identified individually.

My pharmacy is: (Look on your prescription bottle labels)

_____ _____

name address

(Complete a separate page for each pharmacy). This authorization is valid for a period of 90 days from the date of the signature on the document.

Participant

Surname:_____ First name: _____

Signature: _____ Date: _____/_____/_____

Parent or guardian (if less than 18 years old)

I give my consent to _____ to participate in the research project and I attest that he/she is not unwilling.

Surname:_____ First name: _____

In my capacity as _____

Signature: _____ Date: _____/_____/_____

Witness

Surname:_____ First name: _____

Signature: _____ Date: _____/_____/_____

Reserved for the study group:

I, _____, certify to having explained to the above participant the nature of the risks associated with participation in this study, and that person has the right to withdraw at any time. I also gave the assurance that participation would be kept confidential.

Responsible for study:

Surname:_____ First name:_____

Signature: _____ Date: _____/_____/_____

Appendix 5

Hospital RCT information data collection form

CLINICAL TRIAL DATA FORM

Hosp File # _____ Hospital _____ Pt # (Code) _____

Clinical Trial Study _____

Date of screening _____

Date of start in trial _____ Date of end _____

Withdrawal? ☐ no ☐ yes Reason: _____

Severity Criteria

1. Diagnosis of asthma? ☐ yes ☐ no ☐ unknown

2. PT already on inhaled corticosteroids (current)? ☐ yes ☐ no ☐ unknown

3. History of inhaled corticosteroids? ☐ yes ☐ no ☐ unknown

4. Volume % of Predicted? ☐ 1st ☐ 2nd ☐ unknown

4. Comorbidities noted? ☐ yes ☐ no ☐ unknown

Specify: _____

Comments : _____

5. Other?

Hospitalisation during trial:

Date of admission _____ Date discharge _____

PLACEBO/OTHER MEDICATION

Start: _____ End: _____

Date	NAME	Dose	Posology

4. OTHER INTERVENTIONS

Date	Nature	Duration (if applic.)	Comments

6. EMERGENCY DEPARTMENT VISITS

Date	Diagnosis	Duration	Comments

Appendix 6

Pharmacy ambulatory medications data collection form

COUT-EFFICACITÉ 'PRATIQUE' PAR COMPARAISON AVEC COUT-EFFICACITÉ : LORS DE L'ESSAI CLINIQUE DES CORTICOSTEROIDES INHALÉS DANS LE TRAITEMENT DE L'ASTHME

COLLECTE DES DONNÉES
PHARMACIE

PATIENT: NOM :
PRÉNOM :

NUMERO D'ASSURANCE MALADIE :

CODE :

PERIODE DE COLLECTE DES DONNÉES :

DEBUT :

FIN :

NOM DE LA PHARMACIE :

ADRESSE :

IODE DE COLLECTE DES DONNÉES : CODE :

DEBUT :

FIN :

ANT LA PÉRIODE SPECIFIÉE CI-HAUT, EST-CE QUE LA PERSONNE AVAIT UNE ASSURANCE - IBOURSEMENT DES MÉDICAMENTS ?

oui ☐ non ☐

DANT LA PÉRIODE SPECIFIÉE CI-HAUT, EST-CE QUE LA PERSONNE A REÇU LES MÉDICAMENTS SCRITS SUIVANTS ?

ASSE		non	oui	SPECIFIEZ LES NOMS :
00:00	ANTINÉOPLASIQUES (méthotrexate, cytoxan...)	☐	☐	
08:04	ANTIPARKINSONIENS (benztropine, trihexyphénidyle...) ou LÉVODOPA	☐	☐	
12:04	ANTICOAGULANTS (héparine, warfarine...)	☐	☐	
04	CARDIOTROPES (diltiazem, digoxine, métoprolol...)	☐	☐	
6	HYPOLIPÉMIANTS (lovastatine, fluvastatine, gemfibrozil...)	☐	☐	
08	ANTIHYPERTENSEURS (captopril, énalapril...)	☐	☐	
08	ANALGÉSIQUES OU AINS (piroxicam, naproxen, morphine...)	☐	☐	
12	ANTICONVULSIVANTS (phénobarbital, clonazépam, carbamazépine...)	☐	☐	

IODE DE COLLECTE DES DONNÉES : CODE :

DEBUT :

FIN :

ASSE		non	oui	SPECIFIEZ LES NOMS :
.6:04	ANTIDÉPRESSEURS (fluoxétine, sertraline...)	☐	☐	
16:08	TRANQUILLISANTS (halopéridol, promazine...)	☐	☐	
28	DIURÉTIQUES (hydrochlorothiazide, spironolactone...)	☐	☐	
40	DIVERS GASTRO-INTESTINAUX (cimetidine, ranitidine...)	☐	☐	
20	ANTIDIABÉTIQUES (insuline, glyburide...)	☐	☐	
36	THYROIDIENS (levothyroxine, thyroglobuline...)	☐	☐	
TRE	: CYCLOSPORINE	☐	☐	

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES :

CODE : _____

DÉBUT :
FIN :

RAPPORTEZ, POUR LA PÉRIODE SPECIFIÉE CI-HAUT, L'UTILISATION DES CLASSES DE MÉDICAMENTS ANTI-ASTHMATIQUES SUIVANTS . POUR CHAQUE CLASSE, RAPPORTEZ LE NOM DU MÉDICAMENT ET LA POSOLOGIE AINSI QUE LES DATES D'EXÉCUTION DES ORDONNANCES NOUVELLES OU RENOUVELÉS AVEC LA QUANTITÉ DISPENSÉE (VOIR EXEMPLES) :

Sympathomimétiques: (salbutamol, isoprotérénol, fénotérol, ORAUX terbutaline...)

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant
ex: Ventolin 2mg bid.	11/10/92	60	4/11/92	60	5/12/92	60	3/1/93	120	5/3/93	60		

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES : CODE : ______

DÉBUT :

FIN :

Sympathomimétiques en inhalation: (salbutamol, isoprotérénol, fénotérol, terbutaline...)

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant
ex: Ventodisk 100 mcg 2X bid	4/7/93	1	18/9/93	1	5/11/93	1						

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES :

CODE : ______

DÉBUT :
FIN :

Spasmolytiques (oxtriphylline, théophylline, aminophylline)

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES : CODE : ______

DÉBUT :
FIN :

Corticostéroïdes en inhalation: (béclomethasone, budésonide, flunisolide, triamcinolone...)

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES :

CODE : ______

DÉBUT :

FIN :

Ipratropium ou Cromoglycate

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES :

CODE : ______

DÉBUT :
FIN :

Corticostéroïdes oraux : (méthylprednisolone, prednisone...)

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant

UTILISATION DES MÉDICAMENTS ANTI-ASTHMATIQUES

PÉRIODE DE COLLECTE DES DONNÉES : CODE : ______

DÉBUT :

FIN :

Antibiotiques oraux : (céfaclor, érythromycine, amoxicilline, pénicilline 'G'...)

NOM ET POSOLOGIE	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant	Date	Quant

Appendix 7

Inclusion criteria community pharmacy subjects – medication use

Critères d'admissibilité

Patient:

Nom _____ **Prénom** _____

Sexe **M :** ____ **F :** ____

Date de naissance : ___/____/___
jour/mois/année

Adresse : _____ Numéro de téléphone :_____

A. Profil médicamenteux du patient:

Prescription courante ou récente (deux ans ou moins) de corticostéroïde en inhalation*

Oui ☐ **Non** ☐ → non admissible

*Beclovent, Becloforte, Beclodisk, Vanceril, Beclomethasone, Pulmicort (budésonide), Bronalide, Flovent (fluticasone), ou Azmacort

Quatre traitements ou plus de fortes doses de stéroïdes oraux durant quelques jours au cours des 12 derniers mois (prednisone, méthylprednisone)

Oui ☐ → non admissible **Non** ☐

Appendix 8

Inclusion criteria community pharmacy subjects – subject responses – French language

Questionnaire d'admissibilité

1.
Est-ce que vous avez déjà participé dans une étude ou un projet de recherche d'un médicament?

OUI ☐ NON ☐

↓

non admissible
Arrêtez ici et remerciez le patient

2.
Est-ce que votre médecin vous a informé que vous faisiez de l'asthme?

OUI ☐ NON ☐

↓

non admissible
Arrêtez ici et remerciez le patient

3.
Est-ce que votre médecin vous a informé que vous faisiez de l'emphysème?

OUI ☐ NON ☐

↓

non admissible
Arrêtez ici et remerciez le patient

Si le patient a 45 ans ou plus:

4.
Est-ce que vous fumez, ou est-ce que vous avez déjà fumé?

OUI ☐ NON ☐

↓ passez à question 5

5.
Pendant combien d'années avez-vous fumé régulièrement (à tous les jours)?* ☐ années

*Déduire du total les années au cours desquelles la personne ne fumait pas .

6.
Au cours de ces années, combien de paquets par jour avez-vous fumé en moyenne? ☐ paquets

Calculer le nombre de paquets-année (i.e. nombre de paquets par jour X le nombre d'années)

Le patient a-t-il fumé au moins 20 paquets-année ?

OUI ☐ NON ☐

↓ non admissible
Arrêtez ici et remerciez le patient

Questionner le patient sur ses symptômes.

7.

Est-ce que le nombre de vos épisodes de difficultés respiratoires a augmenté depuis les quatre dernières années ?

OUI ☐ NON ☐

↓

non admissible
Arrêtez ici et remerciez le patient

8.

Est-ce que la sévérité de vos épisodes de difficultés respiratoires a augmenté depuis les quatre dernières années ?

OUI ☐ NON ☐

↓

non admissible
Arrêtez ici et remerciez le patient

Demander au patient le type de médicament qu'il utilise en cas de crise d'asthme (bêta-2-agoniste). Demander alors au patient:

9.

Durant la dernière semaine, combien de fois par jour, en moyenne, avez-vous utilisé votre pompe de ....(spécifier laquelle)? _____

10.

Durant la dernière semaine, combien de jours avez-vous utilisé votre pompe plus de 2 fois par jour? _____

11.

Durant la dernière semaine, combien de jours avez-vous eu des difficultés respiratoires suffisantes pour que vous les notiez ? _____

12.

Durant la dernière semaine, combien de nuits vous êtes-vous réveillé(e) à cause de vos difficultés respiratoires? _____

Appendix 9

Inclusion criteria community pharmacy subjects – subject responses – English language

Questionnaire d'admissibilité (English)

1 .
Have you ever participated in a drug research project or study of medical drugs?

YES ☐ NO ☐

↓
not eligible
Stop here and thank the patient

2 .
Has your doctor ever told you that you have asthma?

YES ☐ NO ☐

↓
not eligible
Stop here and thank the patient

3 .
Has your doctor ever told you that you have emphysema?

YES ☐ NO ☐

↓
not eligible
Stop here and thank the patient

If the person is 45 years of age or older:

4 .
Do you smoke or did you ever smoked?

YES ☐ NO ☐

↓
go to question 7

5 .
For how many years did you smoke regularly (daily)?* ☐ years

*Deduct from the total years the number of years during which the person did not smoke .

6 .
During those years, how many packages did you smoke a day (on average)? ☐ packs

Calculate the number of pack-years (the number of packages per day X the number of years)

Did the patient smoke at least 20 pack-years?

YES ☐ NO ☐

↓
not eligible
Stop here and thank the patient

Ask the patient about his symptoms.

7.
Has the number of episodes of breathing difficulties increased over the last 4 years?

YES ☐ NO ☐

↓

not eligible
Stop here and thank the patient

8.
Has the severity of your episodes of breathing difficulty increased over the last 4 years?

YES ☐ NO ☐

↓

not eligible
Stop here and thank the patient

Ask the patient what type of medication he uses in case of asthma attack (beta-2-agonist). Then ask the patient:

9.
Over the last week, how many times per day (on average) have you used your pump...(specify which)? _____

10.
Over the last week, for how many days did you use that pump more than twice a day for two puffs each (i.e., 4 total)? _____

11.
Over the last week, for how many days were your breathing difficulties severe enough for you to notice them? _____

12.
Over the last week, how many nights were you awakened because of your asthma? _____

Appendix 10

Community pharmacy subjects consent forms – French language

HOPITAL DU SACRÉ-COEUR -- UNIVERSITÉ DE MONTRÉAL

Formulaire d'information (pharmacie)

Nom du chercheur Un projet de recherche examinant l'utilisation des soins de santé par des asthmatiques québécois prenant des stéroïdes en inhalation est en cours sous la responsabilité d'un groupe de chercheurs de l'Université de Montréal, dirigé par le Dr. André-Pierre Contandriopoulos, économiste de la santé, Dr. Claudine Laurier, pharmacienne, Dr. Jean-Luc Malo, pneumologue, ainsi que d'une étudiante au doctorat, Wendy Kennedy. Cette étude a été approuvée par les Comités d'Éthique de trois centres hospitaliers: l'hôpital Sacré-Coeur de Montréal, l'hôpital Laval de Québec et l'hôpital Général de Montréal.

But de l'étude Cette étude s'intéresse à l'utilisation des soins de santé dans deux groupes de sujets asthmatiques: ceux de la population générale et ceux qui participent à des essais cliniques. Les indices décrivant l'utilisation des soins de santé sont les hospitalisations, les visites dans les salles d'urgence, les visites aux médecins et les ordonnances de médicaments antiasthmatiques. Les autres médicaments ne seront pas considérés dans l'analyse, sauf pour estimer le présence des autres problèmes de santé.

Procédures de l'étude Si vous acceptez de participer à cette étude, votre implication consistera à identifier vos pharmacies habituelles et à consentir que le groupe de recherche ait accès à l'information de vos dossiers des pharmacies. A cet égard, un membre de l'équipe de recherche pourrait vous contacter, dans les jours qui suivent, pour recueillir le nom de ces pharmacies. Ensuite, certaines informations aux dossiers de la Régie d'Assurance Maladie du Québec et Med-Echo qui contiennent les renseignements relatifs à votre utilisation de soins de santé (par exemple les visites médicales et les séjours hospitaliers) au cours de deux années vont être jumelées. Les renseignements obtenus sont limités à une période de deux ans qui se situera entre le 1er janvier 1988 et le 31 décembre 1996. Pour faciliter cette demande, nous vous demandons de nous fournir votre numéro d'assurance-maladie. Votre numéro ne nous servira qu'à des fins d'études et aucun jugement ne sera porté sur votre utilisation de services.

Risques potentiels Il n'y a en soi aucun risque potentiel associé à cette étude car elle n'implique aucune modification au traitement que vous recevez. Le seul inconvénient, s'il en est, sera de consacrer environ 10 minutes au total pour lire ce formulaire et pour donner l'information.

Bienfaits potentiels Il n'y a pas de bénéfice personnel relatif à cette étude. Par contre, la réalisation de cette étude permettra de mieux connaître l'impact que les problèmes de santé comme l'asthme ont sur le système de santé.

Confidentialité de dossiers Certaines informations sur l'utilisation des services de soins de santé et médicaments pour traiter l'asthme seront puisées de votre dossier de médicaments détenu à votre (vos) pharmacie(s). Tous les renseignements recueillis à votre sujet au cours de l'étude demeureront strictement confidentiels et vous ne serez identifié(e) que par vos initiales et un numéro de code afin de préserver l'anonymat. Toute l'information puisée de votre dossier médical détenu au Ministère de la Santé et des Service Sociaux le sera d'une façon anonyme avec un numéro de code brouillé afin de préserver l'anonymat. Aucune publication résultant de cette étude ne renfermera quoi que ce soit qui puisse permettre de vous identifier. Les informations que nous allons recueillir ne seront utilisées que pour la présente étude. Cependant, votre dossier pourra être consulté par des représentants de l'organisme ou de l'entreprise impliquée et des organismes gouvernementaux de santé autorisés. Deux comités, le Comité des essais cliniques et le Comité d'éthique de recherche de L'Hôpital Général de Montréal peuvent revoir les dossiers de recherche afin d'assurer la conformité avec les réglementations de recherche sur les êtres humains. Tous ces organismes adhèrent à une politique de stricte confidentialité.

Indemnisation En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, les organismes, les entreprises ou les institutions impliqués de leurs responsabilités légales et professionnelles.

Droit d'abandonner l'étude Votre participation est entièrement volontaire. Vous êtres libre de refuser d'y participer. Vous pouvez également vous retirer de l'étude à n'importe quel moment en faisant connaître votre décision au chercheur ou à l'un de ses assistants. Votre refus de participer ou de vous y soustraire à n'importe quel moment n'entraînera pour vous aucune conséquence défavorable sur les soins qui vous seront fournis par la suite. Le chercheur responsable de l'étude peut aussi décider de vous retirer de l'étude sans votre consentement.

Personnes à contacter Si vous avez des questions à poser au sujet de cette étude ou s'il survient un incident quelconque, ou si vous désirez vous retirer de l'étude, vous pouvez contacter en tout temps:

Wendy Kennedy, assistante de recherche, téléphone: 514 343-7365 ou [redacted]

Et si vous avez des questions concernant le protocole de recherche vous pouvez contacter:

M. Glenn Fash, représentant des patients, a l'Hôpital Général de Montréal téléphone: [redacted]

Consentement du sujet

La nature de l'étude, les procédés, les risques et les bénéfices que comporte ma participation à cette étude ainsi que le caractère confidentiel des informations qui seront recueillies au cours de l'étude m'ont été expliqués.

J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et de recevoir des réponses qui m'ont satisfait(e).

Je, soussigné(e), accepte volontairement de participer à cette étude. Je peux me retirer en tout temps sans que cela ne nuise aux relations avec mon médecin, mon pharmacien, et les autre intervenants et ce, sans préjudice d'aucune sorte.

Je reconnais avoir reçu une copie signée de ce formulaire d'information et de consentement.

Je donne l'autorisation au pharmacien dont le nom apparaît sur ce formulaire, de fournir les détails des ordonnances que l'on m'a livrées pour traiter mon asthme à Wendy Kennedy ou Claudine Laurier. Ces renseignements porteront sur une période consécutive de 24 mois à partir du_____ jusqu'au _____, inclusivement.

Mon numéro **d'assurance-maladie** (sur la carte soleil) est:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Mon numéro d'assurance-maladie sera utilisé pour obtenir de l'information de la Régie d'Assurance Maladie du Québec et Med-Echo. Toute information sera regroupé et personne sera identifie individuellement.

Ma pharmacie est:

_____ _____

nom adresse

Cette autorisation est valable pour un période de 90 jours à compter de la date de la signature de ce document.

Participant

Nom:_____ Prénom: _____

Signature: _____ Date: ____/_____/_____

Témoin

Nom:_____ Prénom: _____

Signature: _____ Date: ____/_____/_____

Réservé pour le responsable de l'étude:

Je, _____, certifie avoir expliqué à la personne ci-haut mentionnée la nature et les risques de la participation à cette étude, et que la personne a l'opportunité de ce retirer de l'étude en tout temps. Je l'ai assurée que sa participation sera tenue confidentielle.

Responsable de l'étude:

Nom:_____ Prénom: _____

Signature: _____ Date: ____/_____/_____

Appendix 11

Community pharmacy subjects consent forms – English language

SACRÉ-COEUR HOSPITAL-- UNIVERSITY OF MONTRÉAL

Information Form (pharmacy)

Cost-efficacy vs, cost-effectiveness: inhaled corticosteroids in the treatment of asthma

Researchers' names A research project looking at the use of health services by asthmatics in Quebec taking inhaled corticosteroids is underway directed by a group of researchers at the University of Montreal. The group consists of Dr. André-Pierre Contandriopoulos, Health Economist, Dr. Claudine Laurier, Pharmacist, Dr. Jean-Luc Malo, Pneumologist, as well as a doctoral student, Wendy Kennedy. The study has been approved by the Ethics Committees of three hospitals: Sacré Coeur of Montreal, Laval of Quebec, and the Montreal General Hospital.

Study objective The study explores the use of health services by two groups of asthmatics, those in the general population and those who have participated in clinical studies. The use of health services consists of hospital stays, emergency room visits, physician visits, and prescription drugs to treat asthma. Other drugs are not included in the study, except to estimate the presence of other health problems.

Study procedures If you agree to participate in this study, your involvement consists of identifying the pharmacies which you normally use and granting permission to the research group to have access to your pharmacy file. For the purpose of ascertaining the names of your other pharmacies, a member of the research group will call within the next few days. Afterwards, certain information from the Quebec Health program files which contain the data about your health services utilization, such as physician visits and hospital stays, will be added. The information collected will be limited to a period of two years somewhere between January 1988 and December 1996. To allow us access to this information, we need your health insurance number and the name(s) of the pharmacy(ies) where you purchase your medications. Your health insurance number will be used only for this study, and no judgment will be made of the health services used.

Potential risk There is no risk associated with participating in this study, because it does not imply any change or modification in the treatment you receive. The only inconvenience, if there is any, is to spend a total of approximately 10 minutes reading this form and completing the information requested.

Potential benefit There is no personal benefit associated with your participation in this study. On the other hand, the study will allow a greater understanding of the impact of health problems such as asthma on the health care system.

Confidentiality of the information Information about the use of health services and medications for the treatment of asthma will be extracted from your pharmacy drug file. All the information extracted will remain strictly confidential and you will be identified only by a code number and initials in order to assure anonymity. In none of the publications resulting from the study will you be identifiable in any way. The information extracted will be used only for the purposes of this study. On the other hand, your data files could be consulted by representatives of participating organizations or authorized government health organizations. The hospital Research Ethics and Clinical Trials Committees may review the research records to monitor compliance with Institutional regulations regarding research involving human subjects. All of these organizations adhere to policies of strict confidentiality.

Indemnity By agreeing to participate in this study, you are not giving up any of your rights, nor are you releasing the researchers, the organizations involved, the groups or institutions from their legal or professional responsibilities.

Right to abandon study Your participation is entirely voluntary. You are free to refuse to participate. You can as well withdraw from the study at any time by making your decision known to any one of the researchers or their assistants. Your refusal to participate or your decision at any time to withdraw will have no unfavorable effect on the health care you receive subsequently. The researcher responsible for the study can also decide to withdraw you at any time from the study without your consent.

Persons to contact If you have any questions to ask about the study, or if anything arises or if you wish to withdraw from the study, you can contact at any time:

Wendy Kennedy, research assistant, telephone: 514 343-7365 or [redacted]

Additionally, if there are questions related to the study protocol the following patient representative may be contacted at the Montreal General Hospital:

Mr. Glenn Fash, telephone: [redacted]

Subject's consent

The nature of the study, the procedures, the risks and the benefits which result from my participation in this study, as well as the confidential nature of the information gathered over the course of the study have been explained to me.

I have had the opportunity to ask questions about all aspects of the study and have received satisfactory responses.

I, the undersigned, accept voluntarily to participate in this study. I can withdraw at any time and it will not affect the relationship with my physician, my pharmacist or any of the other intervenants, and results in no prejudice of any kind.

I acknowledge receipt of a signed copy of this information form and consent.

I authorise:

1. the pharmacy whose name appears on this form to supply details of the prescriptions which I have received to treat my asthma,

to Wendy Kennedy or Claudine Laurier. The information released covers a period of 24 consecutive months from _____ to _____, inclusive.

My Health Insurance Number (on the "carte soleil") is:

☐☐☐☐ ☐☐☐☐ ☐☐☐☐

My health insurance number will be used to obtain information from the Quebec Health program files. All information will be gathered on a group basis and no person will be identified individually.

My pharmacy is:

_____ _____

name address

This authorisation is valid for a period of 90 days from the date of the signature on the document.

Participant

Surname:_____ First name: _____

Signature: _____ Date: ____/_____/_____

Witness

Surname:_____ First name: _____

Signature: _____ Date: ____/_____/_____

Reserved for the study group:

I, _____, certify to having explained to the above participant the nature of the risks associated with participation in this study, and that that person has the right to withdraw at any time. I also gave the assurance that participation would be kept confidential.

Responsable for study:

Surname:_____ First name:_____

Signature: _____ Date: ____/_____/_____

Appendix 12

Instructions to community pharmacists for recruiting subjects

Coût-efficacité d'étude clinique vs coût-efficacité d'utilisation réelle corticostéroïdes en inhalation dans le traitement de l'asthme

ISTRUCTIONS À L'INTENTION DU PHARMACIEN

lection des patients

ote: Cette étude inclut les asthmatiques hommes ou femmes; pour simplifier le texte, nous 'ons utilisé le masculin, sans discrimination.

ous trouverez sur la première page du cahier le profil des 15 patients que vous devez cruter. Chaque patient à recruter est décrit en fonction de l'âge, du sexe et de la période ur laquelle des informations sur son utilisation de médicaments sont requises (période sée). Vous devez donc recruter parmi vos patients, une personne qui répond à chacun des ofils établis.

Parmi vos patients actuels

a) qui se présentent à la pharmacie, et,
b) qui ont reçu des corticostéroides en inhalation utilisé pour traiter l'asthme, et non la rhinite, au cours des dernières années *et au cours de la période visée (tel que documenté dans le dossier ou rapporté par le patient)* . *(La liste des corticostéroides en inhalation se trouve en annexe,)*

emander à chaque personne qui correspond au profil décrit sur la liste de la première page si le accepte de participer à l'étude. Compléter la fiche « Critères d'admissibilité » (fiche bleue cluse sous la section « Patients ».

Si la personne accepte de participer, administrer le questionnaire d'admissibilité (jaune) clus dans la section « Patients » et portant sur les symptômes asthmatiques et les habitudes latives à l'usage du tabac. Selon les réponses obtenues, vous assurer de l'admissibilité du atient. (N.B. Vous devez conservez les questionnaires de tous les patients interrogés qu'ils ient admissibles ou non)

Si le patient est admissible, lui remettre, pour lecture et signature, deux exemplaires du rmulaire de consentement (blanc). Avant de lui remettre, compléter chacun des deux emplaire du formulaire en inscrivant sur la troisième page, les dates de la période visée. le patient le désire, il peut compléter le formulaire à domicile et le remettre lors de sa rochaine visite à la pharmacie. Le patient doit conserver un des exemplaires et vous tourner l'autre dûment signé. Vous devez signer chaque exemplaire à titre de témoin.

Suite au retour du formulaire de consentement dûment complété et signé, compléter le mulaire « Collecte de données-pharmacie » (rose). Si vous jugez plus pratique de procéder ısi, vous pouvez fournir un copie du dossier patient pour la période visée plutôt que de npléter les pages 3 à 9 du formulaire.

Pour chaque personne récrutée, compléter l'information sur la première page, incluant le m du sujet.

ANNEXE Liste des corticostéroides en inhalation

Nom générique	Nom de marque	DIN	Dose	Forme	Quantité
Beclo-	Beclodisk	828521	100mcg/coque	Pd aero (8)	15
methasone	Beclovent Rotacaps	545325	0.1mg/cap	Pd Aero	100
	Beclovent Rotacaps	1949993	0.1mg/cap	Pd Aero	100
	Beclodisk	828548	200mcg/coque	Pd aero (8)	15
	Beclovent Rotacaps	545333	0.2mg/cap	Pd Aero	100
	Beclovent Rotacaps	1950002	0.2mg/cap	Pd Aero	100
	Beclodisk + Diskhaler	899127	100mcg/coque	Pd aero (8)	15
	Bec Rota + Rotahaler	895377	0.1mg/cap	Pd Aero	100
	Beclodisk + Diskhaler	899135	200mcg/coque	Pd aero (8)	15
	Bec Rota + Rotahaler	895369	0.2mg/cap	Pd Aero	100
	Beclovent 80 doses	893633	0.05 mg/dose	MDI	1
	Beclovent 200 doses	334243	0.05 mg/dose	MDI	1
	Vanceril 200 doses	374407	0.05 mg/dose	MDI	1
	Beclovent 200 doses	893633	0.05 mg/dose	MDI	1
	Becloforte	897353	0.25mg/dose	MDI(80)	1
	Becloforte	897353	0.25mg/dose	MDI(200)	1
	Becloforte	768707	0.25mg/dose	MDI(200)	1
	Beclomethasone (Altimed)	872334	0.05 mg/dose	MDI	1
Budesonide	Pulmicort Turbuhaler	852074	100mcg/dose	Pd inh (200)	1
	Pulmicort Turbuhaler	851752	200mcg/dose	Pd inh (100)	1
	Pulmicort Turbuhaler	851752	200mcg/dose	Pd inh (200)	1
	Pulmicort Turbuhaler	851760	400mcg/dose	Pd inh (200)	1
	Pulmicort Inhaler	634549	200mcg/dose	MDI(100)	1
	Pulmicort Spacer	898287	200mcg/dose	MDI(100)	1
	Pulmicort Spacer	814091	200mcg/dose	MDI(100)	1
	Pulmicort Inhaler	817228	50mcg/dose	MDI(200)	1
	Pulmicort Spacer	634530	50mcg/dose	MDI(200)	1
Flunisolide	Bronalide (100 doses)	588997	250 mcg/dose	MDI	1
	Bronalide (100 doses)	790486	250 mcg/dose	MDI	1
Fluticasone	Flovent (60 doses)	2174731	25 mcg/dose	Pd inh	1
	Flovent (120 doses)	2174731	25 mcg/dose	Pd inh	1
	Flovent (60 doses)	2174758	50 mcg/dose	Pd inh	1
	Flovent (120 doses)	2174758	50 mcg/dose	Pd inh	1
	Flovent (60 doses)	2174766	125 mcg/dose	Pd inh	1
	Flovent (120 doses)	2174766	125 mcg/dose	Pd inh	1
	Flovent (60 doses)	2174774	250 mcg/dose	Pd inh	1
	Flovent (120 doses)	2174774	250 mcg/dose	Pd inh	1
Triamcinolone,	Azmacort (240 doses)	769983	200mcg/dose	MDI	1
acetonide	Azmacort (240 doses)	1926314	200mcg/dose	MDI	1