Assessment of Compliance Amongst Asthma Patients
Using Anti-inflammatory Medication:
Validating an Instrument Useful in Quantifying Inhaler Consumption
And Identifying Non-adherence – A Pilot Study

by

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A thesis submitted in conformity with the requirements
for the degree of Master's of Science
Graduate Department of Medical Science
University of Toronto

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Assessment of Compliance Amongst Asthma Patients Using Anti-inflammatory Medication: Validating an Instrument Useful in Quantifying Inhaler Consumption And Identifying Non-adherence – A Pilot Study

Master's of Science 2001

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Abstract

Many asthma patients do not adhere regularly to inhaled anti-inflammatory therapy, which is essential in controlling respiratory symptoms and preventing exacerbation in persistent asthma. The purpose of this pilot study was to begin the development of an interview-based instrument, which would estimate medication consumption accurately and detect non-compliance. A questionnaire, based on the literature and expert opinion, was designed and administered orally to recruited asthma volunteers in a semi-structured interview. Questions for which responses significantly correlated with medication consumption, as estimated by the patient's pharmacy record, were fitted into a multiple regression model. The regression model examined the patient's reported anti-inflammatory inhaler emptying rate, estimated forgetfulness with anti-inflammatory therapy and reported time elapsed since short-acting bronchodilator usage. These questions from our regression model were compiled into a revised version of our questionnaire, termed the Asthma Compliance Assessment Survey (ACAS), which had a sensitivity and specificity of 41% and 85% respectively.
Acknowledgements

We would like to thank

The Asthma Society of Canada

and

The Ontario Thoracic Society (Long-term Grant)

for generously funding this project.
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Abbreviations

ACAS  Asthma Compliance Assessment Survey
BID   bis in die, twice a day
CAO   chronic airflow obstruction
CD4+  marker for T helper cells
CD8+  marker for killer T cells
COPD  chronic obstructive pulmonary disease
DOT   directly observed therapy
FEV1  forced expiratory volume in one second
ICS   inhaled corticosteroids
IL-4  interleukin four
IL-5  interleukin five
IL-8  interleukin eight
LTRA  leukotriene receptor antagonist
MDI   metered dose inhaler
PRN   pro re nata, as the occasion arises
PEF   peak expiratory flow
TH1   T helper cell, subset 1
TH2   T helper cell, subset 2
QID   quarter in die, four times a day
### Operational Definitions

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<td>Compliance</td>
<td>&quot;The extent to which a person's behavior (in terms of taking medications, following diets or executing lifestyle changes) coincides with medical or health advice. &quot; (Haynes 1979) Synonyms include adherence and concordance.</td>
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<td>Compliance cut off</td>
<td>A percent value of medication consumption above which a patient is deemed compliant. For example, a cut-off level of 70% is used in this study.</td>
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<td>Compliance rate</td>
<td>Ratio of participants who were deemed compliant with their anti-inflammatory medication as determined by pharmacy records.</td>
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<td>Study population</td>
<td>A group of patients for whom consent to release medical information was obtained and their complete pharmacy data followed a normal distribution.</td>
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<td>Missing data population</td>
<td>Includes patients for whom either medical release consent or complete pharmacy records were not obtained.</td>
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<td>Compliant group</td>
<td>A sub-group of study population patients, who consumed more than 70% of prescribed anti-inflammatory medication as determined by pharmacy records.</td>
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<tr>
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<td>A sub-group of study patients, who consumed less than 70% of prescribed anti-inflammatory medication as determined by pharmacy records.</td>
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<td>No medical release</td>
<td>A sub-group of missing data population patients, who refused to give consent for release of pharmacy records.</td>
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Chapter 1

Introduction

"The absence of reliable, valid, clinically sensitive indices of adherence is an important problem because it can compromise clinical trials, lead to the ordering of unnecessary diagnostic tests or use of alternative medications."

(Meichenbaum and Turk 1987)

This lack of adherence indices also impedes a clinician's ability to detect non-compliance in his or her patients during routine follow-up. Non-compliance among patients with chronic diseases such as asthma is a widespread and persistent problem for clinicians. Unfortunately, recognizing non-compliance is difficult, and no gold standard measurement for compliance exists (Rudd 1977). The main purpose of this pilot study is to initiate the development of an instrument, which would accurately predict respiratory medication consumption and hence estimate compliance in patients with asthma.

Background

The background consists of a literature review divided into two parts. The first part discusses asthma as a disease, including its prevalence, pathogenesis, diagnosis, and treatment. The second part reviews important issues dealing with compliance, including an overview of nomenclature, factors affecting compliance, measurement of compliance and interventions to improve compliance.
PART 1 - ASTHMA

Introduction

The Canadian Thoracic Society characterizes asthma as a chronic disease which is "associated with variable airflow limitation and a variable degree of hyper-responsiveness" (Boulet et al. 1999). In asthmatics, sensitized respiratory airways become inflamed in response to both endogenous and exogenous antigenic irritants. Asthma is managed through the use of anti-inflammatory medication in particular, inhaled corticosteroids, which attempt to control the underlying airway inflammation. Transient symptoms, such as dyspnea, wheeze and cough, are treated with bronchodilators, such β₂-agonists, which relieve asthma symptoms temporarily.

Prevalence

Epidemiological studies have found that Canada follows a global trend of increasing asthma prevalence (Grant et al. 1999). Approximately 2.7 million Canadians suffer from asthma with males under 18 being most affected (Grant et al. 1999). Rates of asthma mortality decreased during the 1990s (Sears 1997), but the number of fatal attacks and emergency room visits did not. Genetic factors, allergies, atopy, exposure to indoor allergens (eg. dust mites) as well as outdoor irritants such as air pollution have all been proposed as possible determinants of the disease (Becklake and Ernst 1997).

Pathogenesis

Genetic susceptibility and environmental exposure induce a helper-T2 lymphocytic (TH2) response in the lung, which leads to activation and recruitment of inflammatory cells (Holgate 1997). Release of pro-inflammatory mediators and cytokines
by these cells, promote the development of airway inflammation which leads to the development of acute phase asthma characterized by reversible airway obstruction (Busse 1998). Sustained activation of pro-inflammatory cells can lead to chronic inflammation. In some patients, chronic inflammation can induce irreversible damage to respiratory epithelium cells resulting in permanent bronchial narrowing due to airway remodeling (Fabbri 1998).

**Airway Inflammation**

A number of inflammatory cells have been implicated as being responsible for the airway inflammation of asthma. The major contributing cells are discussed in greater detail below.

**Mast Cells**

Patients with asthma have been observed to have an increased level of activated mast cells in their airways (Pesci 1993). In response to an antigen, activated mast cells degranulate releasing preformed inflammatory mediators such as histamine and synthesize new pro-inflammatory mediators such as leukotrienes (Wasserman 1994). Histamine contributes to vessel vasodilation and the contraction of bronchial smooth muscle (Wenzel 1988). Leukotrienes are a group of lipids generated from the cleavage of arachidonic acid in the 5-lipoxygenase pathway, which have been associated with neutrophil chemotaxis and activation. As well, these lipids increase smooth muscle tone, vascular permeability and mucous secretion resulting in bronchoconstriction, airway edema and mucous plugs (Busse 1998).
**Eosinophils**

Eosinophils are among the main cells which contribute to airway inflammation in asthma. Upon recruitment into the lung by respiratory antigens, eosinophils become activated, and initiate injury to lung tissue and airway epithelium through the release of inflammatory mediators, granular proteins and cytokines (Busse 1998). Eosinophils also intensify airway hyper-responsiveness and the level of pulmonary eosinophilia tends to be directly proportional to the severity of the asthma (Bousquet 1990).

**Lymphocytes**

Biopsy and bronchial lavage investigations have suggested that lymphocytes, notably CD4+ T-cells, may be involved in airway inflammation (Busse et al. 1995). In particular, a subset of CD4+ lymphocytes, classified as TH2 may be especially important. TH2 lymphocytes can act on both mast cells and eosinophils through the release of IL-4 and IL-5 respectively (Busse 1998). CD8+ T-cells and the TH1 subset of CD4+ lymphocytes do not seem to play a major role in asthma inflammation.

**Neutrophils**

Recently, neutrophils have been thought to play a role in severe "steroid-resistant" asthma, but their specific function in its pathogenesis is still unclear (Cox 1998). By secreting Interleukin-8 (IL-8), neutrophils may be involved in the chemotaxis of eosinophils and their subsequent degranulation. They may also contribute to airway inflammation in asthmatics, but it appears that this "neutrophilic" inflammation is not sensitive to corticosteroid treatment, in marked contrast to the inflammation produced by eosinophils (Jatakanon, et al. 1999). Release of pro-inflammatory cytokines and
enzymes has been proposed as a possible mechanism of action by which neutrophils induce this inflammation. Neutrophils may also be responsible for the airway obstruction observed in COPD patients (Balzano et al. 1999, Lacoste et al. 1993).

**Diagnosis**

As suggested by Boulet et al. in the Canadian asthma consensus report 1999, the diagnosis of asthma should take under consideration the following three factors: patient symptoms, fluctuating airflow limitation and airway inflammation. Starting with the latter, many methods have been used to assess asthmatic inflammation including bronchial biopsies, bronchial lavage, induced sputum samples, quantification of exhaled nitric oxide, and peripheral blood markers (Bousquet et al. 1998, Gustafsson 1998, Vignola et al. 1998). However, these methods have not yet become a part of routine clinical practice and are currently used only for research purposes. As mentioned earlier, patients with asthma experience symptoms such as shortness of breath, wheezing, chest tightness and cough. Symptomatic patients should undergo objective pulmonary function testing in order to confirm a diagnosis of asthma. Spirometry analyzes lung volumes and airflow, including the maximum volume of air expired in one second (FEV1). Reversible airway obstruction compatible with asthma is considered to be present if FEV1 increases more than 12%, following administration of a beta2-agonist (Boulet et al. 1999). In the absence of bronchoconstriction, variable airflow obstruction can be documented through a provocative testing, such as a methacholine challenge (Martin et al. 1997). In response to a respiratory irritant or bronchoconstrictor, such as methacholine, hypersensitive airways constrict producing asthma symptoms (Boulet et
al. 1999). Another investigation, which is useful in assessing airway obstruction, especially in home monitoring, is peak expiratory flow. A change of more than 20% from baseline readings is considered compatible with the diagnosis of asthma (Boulet et al. 1999).

**COPD vs. Asthma**

Asthma is a disease of chronic airflow limitation along with Chronic Obstructive Pulmonary Disorder (COPD). Due to the similarities in treatment between the two illnesses it is possible that the population recruited for this study contained some patients who in fact had COPD rather than asthma. Therefore, a brief description of COPD is provided below. Chronic Obstructive Pulmonary Disorder (COPD), is characterized by a irreversible or partially irreversible chronic airway obstruction, which, unlike asthma, does not correct even at “maximal medical therapy given over a period of time” (Burrows 1990). Approximately 750,000 have the disease and the annual mortality rate from COPD in Canada is 2.6% (Lacasse et al. 1999). Emphysema and chronic bronchitis are two main categories of COPD, although the two diseases or processes usually coexist in individual patients. The chronic airflow limitation of COPD arises from the loss of lung elastic recoil, the diffuse narrowing of respiratory bronchioles, thickening of airway mucosa, mucous inspissation and airway smooth muscle hypertrophy (Thurlbeck 1990). The main predisposing risk factor for COPD is cigarette smoking but genetic factors such as alpha1-antitrypsin deficiency are thought to increase patient susceptibility (Subramanian and Guntupalli 1994). In addition to education and smoking cessation programs, the treatment of COPD includes use of bronchodilators such as ipratropium
bromide, beta2-agonists, theophylline as well as anti-inflammatory corticosteroids in selected settings (Ferguson 1998).

**Evaluation of Asthma Severity**

At the moment, there are several different expert recommendations on how to measure or define asthma severity. The Canadian Asthma Consensus Report suggests that a combination of bronchodilator usage, percent of predicted FEV1, frequency of symptoms, and morbidity can be used as an indicator of disease severity (Boulet et al. 1999). However, others recommend that asthma severity should be assessed based on the “minimum medication required to maintain control of asthma” (Cockcroft and Swystun 1996), not on the day to day level of disease activity. More objective indicators of asthma severity such as level of pulmonary eosinophilia (Bousquet 1990) and the dosage of methacholine needed to induce a 20% decrease in FEV1, have also been suggested.

**Treatment of Asthma**

As mentioned in the introduction, asthma is treated with two types of medication: relievers and controllers. Relievers consist of bronchodilators, such as β2-agonists and ipratropium bromide, which temporarily relieve asthma symptoms by increasing airway calibre. Controllers, on the other hand, treat the underlying cause of asthma and consist of anti-inflammatory medications such as corticosteroids, leukotriene-receptor antagonists (LTRA) and the so-called non-steroidal chromones – sodium cromolyn and nedocromil (Lipworth 1997, Boulet et al. 1999). According to the Canadian Asthma Consensus Report recommendations, very mild asthma is best treated with a short-
acting β-2 agonist such as salbutamol inhaled on an as needed basis (pm). If a bronchodilator is required more than three to four times a week for the relief of symptoms, then an inhaled corticosteroid, such as beclomethasone dipropionate, should be added and used regularly. Other medications such as long-acting bronchodilators and LTRAs, can be added to the treatment regimen if moderate doses of corticosteroids fail to control asthma symptoms (Boulet et al. 1999). Oral steroids, like prednisone, may be required in the treatment of severe asthma. Inhaled corticosteroids, in general, work well to control asthma but only if taken as prescribed. Unfortunately, many patients do not adhere to recommendations for twice daily self-administration of inhaled corticosteroids and may suffer from poorly controlled asthma as a consequence (Tattersfield 1997).

PART 2 - COMPLIANCE

Introduction

Despite advances in our understanding of asthma and the availability of a wide variety of effective medications for its treatment, many patients still experience poorly controlled asthma. One reason for this is often poor compliance with preventive anti-inflammatory therapy. Compliance is defined as the "extent to which a person's behaviour coincides with medical advice" (Haynes 1979). In recent years compliance has been labeled as an archaic term implying that patients are merely "passive conformists" following "doctor's orders" rather than equal partners with their physician, taking an active role in their well-being (Cramer 1991, Marinker 1998). As a result "modernized " terms such as adherence, concordance and co-operation have been suggested as alternatives since they more accurately reflect the doctor-patient relationship today (Schmier and
Leidy 1998, Marinker 1998). While important, the debate over proper nomenclature, however, does not bring investigators any closer to resolving the fundamental issue - compliance and its lack thereof. Therefore, for simplicity, the terms compliance and adherence will be used interchangeably throughout this document.

Compliance with asthma therapy is traditionally expressed in one of two ways (Chapman et al. 2000). Firstly, compliance can be calculated as a percentage of prescribed medication taken as determined by a gold standard of measurement, such as pharmacy records, which is the method by which compliance is computed in this study. Secondly, the percentage of days on which the correct dosage was taken can also be used to quantify compliance. For the former method, studies have used various compliance cut-off levels ranging from 50-85% (Cochrane 1996, Eisen 1991). For example, one study may designate patients taking 80% of prescribed medication as compliant, while another may set that level at 75%. It seems that most cut-off levels are chosen at the discretion of the researcher. Sackett et al. (1976) did, however, attempt to justify a compliance cut-off level of 80% for anti-hypertensives, through a linear regression comparing clinical outcome to compliance. Unfortunately, there does not appear to be such a benchmark in the literature for asthma compliance studies. Therefore, an arbitrary value of 70%, a crude average of the reported cut-off levels above, was chosen for this study.

Compliance and Chronic Disease

In contrast to an acute disease, a chronic illness can be defined as a condition "[requiring] ongoing medical attention, [persisting] for a long time, and either [resulting] in
limitations in everyday functioning or [has] the potential of poor medical outcome if untreated" (Maly et al. 1999). Examples of chronic conditions include hypertension, heart disease (in particular angina and heart failure), diabetes, epilepsy as well as chronic pulmonary diseases such as asthma and COPD. Long term medication compliance in chronic disease is estimated to be approximately 50% (Cochrane et al. 1999) and some have suggested that less than 30% of treatments are taken as prescribed (Home and Weinman 1999). Previous research has shown that compliance decreases over time (Rand et al. 1995) making adherence an important issue in dealing with chronic disease.

Compliance and Asthma

As a chronic disease, asthma requires ongoing, regular treatment and medical attention. Unfortunately, as with other chronic conditions, compliance with inhaled respiratory medication is low. Past studies have estimated adherence to be between 25-50%, although extremes of 15% and 70% have also been reported (Bender et al. 1997, Wamboldt 1998). Braunstein et al. (1996) used an electronic monitor to assess compliance with inhaled nedocromil sodium over a 12-week period and found the adherence rate to be approximately 35%. Another study, by Chmelik and Doughty (1994) also monitored anti-inflammatory medication usage by means of an electronic device and reported compliance to be approximately 40% despite a comprehensive educational program.

Unlike most other chronic diseases, asthma treatment is further jeopardized by a problem of inadvertant non-compliance. Metered dose inhalers (MDI), are the mainstay of asthma treatment and delivery of adequate medication relies on a proper inhalation
technique used by the patient. Therefore, even when a patient is regularly self-administering his or her inhaler, he or she may still not be depositing sufficient amounts of medication in the lung due to poor MDI technique (Chapman 1998). This is in contrast to orally administered treatment, where compliance is equivalent to medication intake. A further complication arises as a result of the episodic nature of asthma. Rather than regularly inhaling their anti-inflammatory medication, patients may cease to comply with their treatment regimen during symptom-free periods (Chapman et al. 2000).

Compliance Measurement

Many methods have been used or proposed to measure compliance, from biochemical assays to patient dairies. Each method has its advantages and disadvantages, and no “perfect” assessment technique exists. Current methods can be classified into 2 categories, direct or indirect compliance measurement. In contrast to indirect compliance measurement, a direct calculation relies on an “objective” computation of compliance, which is not based on human influence and is, therefore, not subject to individual bias. The two groups are discussed in further detail below.

Direct Measurement

Biochemical measurement is used to measure the concentration of medication or its metabolite in the blood, urine or saliva. While this measurement results in an accurate evaluation of patient drug levels at that particular time, it gives no indication of overall compliance and can be confounded by factors such as diet, other drug use or variations in patient metabolism (Bender et al. 1997). As well, in addition to being invasive, regular monitoring of adherence with biochemical assays can prove to be expensive (Wright
Moreover, it is not a practical method of assessment in asthma, since inhaled medication results in low concentrations of the drug being absorbed into the body (Cochrane 1996).

Another direct way to monitor compliance is through direct patient supervision, which includes methods such as scrutinizing inhaler technique and directly observed therapy (DOT), where every dose is taken in the presence of a health care worker (Schemier and Leidy 1998). For obvious reasons, this approach would be difficult to administer and hence, not feasible in today’s health care environment. While inspection of inhaler technique and observation of medication usage, could be administered from time to time, such permanent arrangements would be impractical.

**Indirect Measurement**

Although they are currently not widely utilized, electronic monitors for inhalers such as the Chronolog (Spector and Mawhinney 1991) and the Doser (Simmons et al. 1998) have been proposed as novel instruments in facilitating the assessment of adherence. While these devices are unable to determine whether a dispensed dose was actually consumed by the patient, they can record precisely when (date and time) a “puff” was actuated. This ability to monitor the time interval over which doses were dispensed allows the identification of patients who completely empty their inhaler canisters all at once in an attempt to appear compliant (Bender et al. 1997, Hamid et al. 1998). Known as “dumping”, this phenomenon is a major drawback to the use of canister weight as a compliance assessment tool.
Weighing inhalers, the equivalent of counting pills in patients treated orally, has also been used in compliance assessment for inhaled asthma therapy. Even though a patient's canister weight decreases the appropriate amount over time, one still cannot prove that the dispensed medication was inhaled by that particular patient using a proper technique. Additionally, this method is unable to show when the inhaler was actuated, and hence canister weight measurement is susceptible to the dumping phenomenon described earlier (Schemier and Leidy 1998).

Pharmacy refill rates can provide useful information when studying compliance. However, the first barrier to the successful implementation of this technique is whether the prescription is filled in the first place. Approximately 30% of patients fail to fill their prescription. More than half of such patients describe the prescription as being "unnecessary" (Levy 1991). Even if the prescription is filled and refilled, it is not possible to determine whether the medication itself was taken properly (Saunders et al. 1998). Patients may also use numerous pharmacies so that pharmacy data may not reflect the "true" number of canisters obtained by the patient. As well, use of multiply canisters at a time, one in a different location or the stockpiling of medication can lead to a "false" estimate of adherence (Saunders et al. 1998).

At first glance, patient self-reports and diaries may seem to be the easiest way to assess compliance, but a misleading estimate can be obtained through this method. Patients often overestimate their compliance in order to please their healthcare provider (Rand et al. 1992, Cochrane 1996). A study by Spector et al. (1986) compared patient written self report with recorded actuations on the Chronolog and showed that diaries
frequently overestimate compliance. With quick relief bronchodilator medication, patients typically under-report their usage (Spector and Mawhinney 1991, Yeung et al. 1994). Physicians, who depend only on their clinical judgement, are poor at compliance assessment. Several studies report physicians ability to predict compliance is no better than chance (Caron and Roth 1968, Mushlin and Appel 1977).

Factors affecting Compliance

Why patients fail to adhere to their treatment regimen has been the subject of numerous studies. Compliance is influenced by a multitude of factors, the dissection of which is a complex process. In the past, studies have shown that adherence is not related to age, gender or socioeconomic status (Hamid et al. 1998, Home and Weinman 1999). However, other studies have suggested that compliance is more likely for older women with higher income and education (Spector et al. 1986, Rand et al. 1995, Apter et al. 1998). Hyland (1998) suggests that financial costs of medication may influence compliance. The severity of a patient's asthma has also not been linked to compliance in some previous studies (Mann et al. 1992, Apter et al. 1994). However, Spiker (1991) suggests that disease severity may be related hyperbolically to compliance, where adherence is low for mild and very severe disease, and higher for moderate severity. Also, a change in asthma severity has not been linked to increased compliance (Mann et al. 1992).

Past studies have associated the complexity of a treatment regimen with noncompliance. Dosing frequency has been found to be inversely proportional to compliance (Rand 1998). Eisen et al. (1990) studied 105 patients on long term anti-
hypertensive medication and reported a difference of 25% in compliance between once a day versus three times daily treatment regimens. A study by Chmelik and Doughty (1994) looked at 20 patients with asthma and found compliance to be 81% and 27% for bid and qid schedules respectively. It seems reasonable that patients would be more likely to remember to take their inhaler twice a day, rather than at several, probably inconvenient, times during the day. There has also been some evidence linking lower compliance with inhaled medication. A prior study (Kelloway et al. 1994) compared the compliance of inhaled versus oral bronchodilator and reported that patients were more likely to be compliant with their oral medication.

Patient awareness of compliance monitoring can also have an impact on their compliance (Simmons et al. 1996). Cochrane (1995) reports that patient adherence changes when patients know that their compliance is being monitored. An interesting study of 30 asthmatics on ICS by Yeung et al. (1994) investigated the effect of electronic monitoring on compliance. Participants, who were aware that their MDI was being monitored, had higher compliance than their blinded counterparts. As well, the “aware” patients more accurately reported inhaler usage on a diary card, while for blinded patients there was a significant difference between self reported and electronically monitored compliance. Additionally, the study also found that patients under-reported bronchodilator usage even though they were aware of compliance monitoring.

Other factors which may influence compliance include quality of life and patient concerns about their medication. In a 1998 study, Boulet investigated the prevalence of “corticophobia”, the fear of inhaled corticosteroids, in the Canadian population. In
telephone interviews of 600 asthmatics, he found that 53% of respondents were concerned about inhaled steroids, and 46% reported being reluctant to use them regularly. Seventy-five percent of participants had not discussed their concerns with their physician. Another study by van der Palen et al. (1997) also indicates that patients are concerned about and reluctant to take ICS. Taking such information under consideration it is not implausible to suggest a link between medication concerns and compliance. Home and Weinman (1999) looked at four chronic illnesses, including asthma and found that adherence as reported by the patient correlated inversely to concern about medication, meaning that those patients with higher reported concerns had lower reported compliance. Research into the impact of quality of life on asthma and compliance is scarce (Cochrane 1996, Jones 1998). Hyland (1998) reports that quality of life may be related to lung function and suggests that quality of life assessment may be useful in managing asthma patients.

Compliance and Sleep Disturbance

Past research has explored sleep disturbance in people with asthma. A 1993 British study by Fitzpatrick et al. reported that at least 80% of asthmatics experience disease related nocturnal awakenings “at least occasionally”. As well, asthma patients were also more likely than controls to find their sleep “unrefreshing”. Similarly, van Keimperna et al. (1995) found that patients with stable asthma have a poorer quality of sleep and reduced mental fitness during the day when compared to controls. Decreased mental fitness, as shown by memory and concentration tests, has also been demonstrated in children (Stores et al. 1998). It could be possible that these sleep
disturbances are related to nocturnal asthma symptoms. Fix et al. (1997) examined the association between nocturnal asthma and disease severity. The study found that disease severity, as reported by patients on a questionnaire examining the frequency of asthmatic symptoms, and the degree to which it interfered with daily activities, correlated significantly with nocturnal asthma. This finding insinuates that nocturnal asthma may be a predictor or marker of poorly controlled asthma. Poorly controlled asthma may come about as a result of low compliance with anti-inflammatory inhalers designed to control airway inflammation. However, the issue may be more complicated. Asai et al. (1991) observed abnormal breathing patterns in Japanese children, who were reported as having stable asthma. This suggests that sleep disturbance may be unrelated to disease control, instead reflecting an underlying breathing pattern abnormality. Therefore, at the present time no concrete evidence is available to link poor compliance with an increase in sleep disturbance.

Compliance Improvement

Patient education may play an important role in improving compliance (Cramer 1991, Barnes 1998). Edworthy et al. (1999) found that "appropriate medication utilization" with an anti-inflammatory medication was higher in arthritis patients receiving "computer assisted educational intervention" when compared to controls. A study by Peckham et al. (1998) showed that compliance with at home oxygen therapy increased 38% with a training program. However, Chmelik and Doughty (1994) found a compliance rate of only 40% for anti-inflammatory medication in those with asthma despite patients participating in an education program. In addition to individual instruction,
Bone (1996) suggests that group education may be beneficial in combination with a good relationship between patient and physician.

Good communication between patient and physician is essential in improving treatment compliance especially in a chronic disease such as asthma. In order to enhance compliance, Geppert and Collazo (1998) recommend an ongoing patient-physician partnership involving the physician in patient education through long-term follow-ups. They also advise physicians to ask “compliance-promoting questions”, such as “do you have any concerns about your medicines?” Mellins et al. (2000) highlights the importance of providing written instructions and charting a long term plan as well as tailoring the treatment regimen to coincide with the patient's daily activities. Furthermore, Steele et al. (1990) found that how one questions a patient about medication usage is essential for identification of non-compliance - “A nonaccusatory, open-ended, information-intensive approach can be a sensitive and productive tool for the diagnosis of a patient's adherence status.” (Steele et al. 1990)
Study Objectives

The development of an assessment tool for compliance is the ultimate objective of this research. Such progress would facilitate a physician’s task in assessing compliance and it would allow physicians to quantify more accurately a patient’s adherence to a treatment regimen during the medical interview. The primary objectives of this initial study is to evaluate the prescription refill rate, the length of time the medication lasts, the estimation of inhaler fullness and patient reported daily consumption as predictors of compliance. As well, we would like to examine the ability of physicians to estimate patient adherence. For our secondary objectives, open-ended questions exploring issues such as patient perception of their asthma and beliefs about their medications will be investigated to detect differences in responses between compliant and non-compliant patients.

RESEARCH QUESTIONS

Research Questions Related To Primary Objectives

1. Does a patient’s reported prescription refill rate, as assessed by the question “When was the last time you refilled your prescription?” accurately predict patient compliance as determined by pharmacy records?

Corresponding question in questionnaire #13
2. Does a patient's reported inhaler emptying rate, as assessed by the question "How long does a canister of your inhaler last?" accurately predict patient compliance as determined by pharmacy records?

   Corresponding question in questionnaire #14

3. Does a patient's inhaler, when assessed for level of fullness, correlate inversely with patient compliance as determined by pharmacy records?

4. Does a physician's estimate of inhaler compliance correlate with patient compliance as determined by pharmacy records?

5. Does a patient's reported daily consumption of inhaled medication, assessed by questions 5, 19 and 26, accurately predict patient compliance as determined by pharmacy records?

   Corresponding questions in questionnaire:
   
   #5  "When was the last time you took your anti-inflammatory/bronchodilator medication?
   #19 "Everyone forgets to take their medication sometimes. What percent of doses do you estimate you have forgotten?"
   #26 "How often do you take your anti-inflammatory/bronchodilator medication?"

Research Questions Related To Secondary Objectives

6. Is there a difference between compliant and non-compliant patients with respect to reported problems taking the prescribed anti-inflammatory/bronchodilator asthma medication as assessed by our questionnaire?

   Corresponding questions in questionnaire:
   
   #10 "Have you had any problems taking your medication?"
   #23 "What don't you like about taking your medication?"
7. Is there a difference between compliant and non-compliant patients with respect to perception of disease severity as assessed by our questionnaire?

   Corresponding questions in questionnaire:
   #7 “How severe do you think your asthma is?”
   #25 “Recently have you noticed any change in the severity of your asthma?”

8. Is there a difference between compliant and non-compliant patients with respect to financial circumstances as assessed by our questionnaire?

   Corresponding questions in questionnaire:
   #12 “What is your opinion on the cost of asthma medication?”
   #15 “How often do you obtain samples of inhaled medication from your physician?”
   #16 “Do you have a drug plan?”

9. Is there a difference between compliant and non-compliant patients with respect to a patient's perception of assistance received in explaining correct anti-inflammatory inhaler usage as assessed by our questionnaire?

   Corresponding questions in questionnaire:
   #17 “Is your physician helpful in explaining how to use your medication?”
   #18 “Is your pharmacist helpful in explaining how to use your medication?”

10. Is there a difference between compliant and non-compliant patients with respect to the patient's concerns about his or her condition as well as the patient's perception of quality of life as assessed by our questionnaire?

   Corresponding questions in questionnaire:
   #22 “Do you have any concerns about having asthma?”
   #24 “Do you think your asthma affects your quality of life?”
11. Is there a difference between compliant and non-compliant patients with respect to sleep disturbance as assessed by our questionnaire?

Corresponding questions in questionnaire:

#29 "Do you feel your asthma interferes with your ability to get a good night's sleep?"

#30 "Does your asthma prevent you from sleeping?"

#31 "Do you feel well rested in the morning?"

**Hypotheses**

We hypothesize that compliance will be accurately predicted by patient reported prescription refill rate, inhaler emptying rate and canister assessment as described in the primary objectives. In accordance with the literature, we predict that neither research question 4 nor 5 will produce a significant result. With respect to the secondary objectives, we predict that there will be no difference between compliant and non-compliant patients for the following research questions: 7 (perception of disease severity), 8 (finances), 11 (sleep disturbance). However, we predict that a significant difference between compliant and non-compliant patients will be found on the remaining research questions: 6 (reported problems taking medication), 9 (assistance in proper inhaler technique) and 10 (concerns regarding disease).
Chapter 2

Method

In general, the above stated research questions (1-11) were incorporated into a 31 item questionnaire which was administered by an interviewer to recruited volunteers. Patient responses to this questionnaire were then compared to our gold standard of compliance measurement – the last refill cycle for anti-inflammatory medication in the patient's pharmacy records as defined below. Questions for which a correlation with pharmacy records was found were subsequently condensed into a revised version of our questionnaire, termed the Asthma Compliance Assessment Survey (ACAS), which is described in greater detail in the discussion.

Subjects and Setting

Asthma patients over the age of 16 with disease of varying severity and levels of control were recruited from respirology and primary care asthma clinics, namely the Toronto Western Hospital's Asthma Centre and the Primary Care Asthma Clinic at Dufferin-St.Clair. Potential study participants were identified by the researcher through a chart review. All patients were required to be prescribed an inhaled anti-inflammatory medication such as corticosteroids, nedocromil sodium or cromoglycate as well as an inhaled short-acting bronchodilator. Patients on additional and/or adjuvant therapies such as long-acting inhaled bronchodilators were not excluded. Reasonable mental capacity and good language skills, as defined by the patient's ability to read and comprehend the consent forms as well as the ability to respond verbally to the questionnaire of their own
accord without the assistance of a third party, were necessary. Patients who required a translator were excluded. The inclusion and exclusion criteria are defined below:

**Inclusion Criteria**

- Patient age greater than 16
- Chart reviewed asthma patients with a wide spectrum of disease severity and control
- Patients prescribed inhaled anti-inflammatory therapy
- Ability to understand verbal and written English
- Reasonable mental capacity

**Exclusion Criteria**

- Patients not prescribed inhaled anti-inflammatory therapy
- Mainstay of treatment consisting of oral rather than inhaled therapy
- Patients taking nebulized medication
- Patient requiring a translator
- Poor mental capacity

**Study Design**

On the day of their appointment with the attending physician, potential study patients were approached in the waiting room by the researcher and invited to participate in a brief, confidential 10-minute questionnaire-based structured interview, which was administered orally before their appointment in a private room. Research personnel read the questions to participants and recorded corresponding responses on the questionnaire form. Upon completion of the questionnaire, consent was obtained for the release of pharmacy records and for patients who had their inhalers with them, canister weight was estimated. Only those patients who signed the medical information release form and for whom completed pharmacy records were collected were included in the study population analysis.
Research Ethics

The questionnaire, along with a patient consent form and a medical information release form, were submitted on November 9, 1998 for approval by the Ethic's Committee at The Toronto Hospital. Tentative verbal approval for the project was obtained on the condition that the medical information form would be revised. A rephrased medical information release form was submitted immediately. Final written approval for the study was sent on December 4, 1998, a copy of which is included in Appendix E.

It should be noted that a patient was given a study consent form after agreeing to the researcher's initial invitation. This study consent form was read and signed by the patient prior to the administration of the questionnaire. Upon completion of the questionnaire the patient was given a medical information release form, and s/he was informed that the release of pharmacy records to the researcher was optional. All patients were advised that all components of the study were optional and they were free to withdraw their participation at any time without consequence.

Canister Fullness Estimation

Once the questionnaire was completed, canister fullness was estimated for those patients who had their inhaler(s) on hand. Actual canister weights were not used because the goal of this study was to develop a practical technique that could be used by health care professionals in an ambulatory setting without special equipment. A researcher, who had previously been trained in such estimation using inhalers of known fullness, carried out the canister estimation. Through manual manipulation such as shaking an MDI canister or dismantling a Turbuhaler to observe its dose wheel, the
researcher was able to estimate the level of inhaler fullness classifying it into one of five fullness categories: 100%, 75%, 50%, 25%, 0% (empty). Subsequently, the date the inhaler was prescribed was noted, as well as the date on which the questionnaire was administered. The number of puffs per day taken by the patient was calculated using the formula below:

\[
\frac{\text{Number of doses in canister} \times (100\% - \text{Estimated canister fullness})}{\text{Number of days between date of Rx and date of survey}} = \text{Estimated puffs/day}
\]

For example, a patient with a Beclomvent® inhaler (200 doses) dispensed 25 days ago, and estimated to be 50% full would be estimated to be taking 4 puffs per day.

In order to assess the reliability of this measurement, canister estimation was repeated upon conclusion of the study using five canisters of Ventolin® (salbutamol), each of which contained 200 doses initially. Doses were dispensed from these inhalers in such a manner, which attempted to simulate actual patient usage. Vigorous shaking of the inhaler was followed by two actuations, separated by five seconds. Each pair of actuations was then succeeded by a 30 second time interval, just prior to the inhaler being shaken vigorously again. This pattern continued until the resultant canisters were obtained as shown below:
<table>
<thead>
<tr>
<th>Canister Code</th>
<th>Number of Doses Dispensed</th>
<th>Percent Full</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>B</td>
<td>50</td>
<td>75%</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>50%</td>
</tr>
<tr>
<td>D</td>
<td>150</td>
<td>25%</td>
</tr>
<tr>
<td>E</td>
<td>200</td>
<td>0%</td>
</tr>
</tbody>
</table>

NB: The above information is based on the assumption that no more than 200 doses were contained in each canister. However, it is possible that a canister may have contained slightly more than the 200 doses indicated on the label.

These inhalers of known fullness were then used to test the consistency with which blinded volunteers estimated canister fullness. After being allowed the opportunity to inspect and become accustomed with the weights of each canister, volunteers were blinded and randomly handed the canisters for fullness estimation, with no time constraints. An observer recorded each volunteer’s estimation of canister fullness. In total 100 trials were carried out on 6 volunteers. The first 50 trials were testing the performance of the researcher who was involved in the original canister fullness estimation in this study. The subsequent 50 trials (ten per volunteer), were completed by a variety of medical personnel, namely two clinicians, an asthma nurse educator, a researcher and a medical student.

Patient Questionnaire

Our original questionnaire consisted of 31 questions and is attached in Appendix A. The questionnaire was designed based on our study objectives, research questions
and extensive literature search. To ensure content validity the questionnaire was reviewed and revised by two clinicians as well as a nurse educator specializing in asthma. The questions were written in understandable everyday language for maximum participant comprehension. Three questions were added in as a distraction in order to prevent patients from postulating the objective of the questionnaire and modifying their answers accordingly. Concurrent criterion validity was assessed by comparing patient responses to our questionnaire with our gold standard of compliance measurement in this study – the last refill cycle for anti-inflammatory medication in the patient’s pharmacy records.

Physician Assessment

For each patient participating in the survey, completion of an evaluation form rating the patient’s compliance was requested from the attending physician. The form, attached in Appendix A, indicated how many puffs per day (or week) the patient reported he or she consumed for each medication and asked the physician to estimate the actual number of puffs per day (or week) he or she thought the patient was taking. In total compliance assessment was obtained from 6 physicians, 5 of whom were blinded to the purpose of our study.

Pharmacy Records

With permission, a record of the patient's refill habits was obtained from the pharmacy and served as a 'gold standard' measure of compliance among patients. Data were collected and examined by a method similar to that described in Saunders et al.
(1998). Pharmacy records for the last 12 months were extracted for each patient and prescription information included the inhaler type, prescription date, number of canisters dispensed and the number of doses per canister. Compliance with inhaled anti-inflammatory medication was calculated using the last refill cycle of each pharmacy record, where a refill cycle is defined as the number of days between two consecutive prescriptions. By using the last refill cycle to calculate compliance, the information obtained for each patient was most current to the time the questionnaire was administered. The formula which calculates consumption of medication for a refill cycle is as follows:

\[
\text{Number of inhalers prescribed} \times \text{Number of puffs per Inhaler} \div \text{Number of days between prescriptions} = \text{Estimated Puffs/day}
\]

The above formula assumes that all the medication was used before the prescription was refilled. If pharmacy records contained no second refill or if the medication and/or dose for a subsequent refill was different, the pharmacy information was deemed as incomplete and hence the patient's data were not used in the analysis. At the time of pharmacy information disclosure, patients were asked to list all the pharmacies from which they obtain prescriptions. Data for patients using multiple pharmacies were compiled together and arranged according to date with information for the last refill cycle being extracted. The daily medication consumption (puffs/day) was calculated for both anti-inflammatory as well as bronchodilator medication. Because most
short-acting bronchodilators are usually prescribed on a pm basis, only compliance for 
the estimated daily consumption of anti-inflammatory medication was calculated based 
on the following formula:

| Daily consumption of anti-inflammatory medication as determined by pharmacy records (puffs/day) | \( \times 100 = \% \) compliance |
| Daily consumption of anti-inflammatory medication as reported by patient in questionnaire (puffs/day) |

Percent compliance for each participant was obtained using the above formula 
and those patients who were calculated as taking more than 70% of their anti-
inflammatory medication were deemed compliant, while those taking less than 70% were 
classified as non-compliant.

Data Analysis

The patient population was first scrutinized for outliers based on extracted 
pharmacy data. This was accomplished using percent compliance as determined by 
pharmacy records for each patient through a boxplot analysis. Responses to our 
questionnaire were then analyzed for the remaining patients. All variables were analyzed 
with descriptive statistics.

Those questions for which continuous data were collected, patient responses 
were graphed in a scatter plot against the patient’s pharmacy records. The 
corresponding Pearson’s correlation coefficient was calculated. Please note that some of 
the answers were first converted to an estimated value in puffs per day (eg. question 
13,14,19). This daily dose was obtained by dividing the maximum number of doses per
inhaler by the patient’s response converted into days. For instance, a patient who reported that they refilled their Flovent® (120 doses) prescription 2 months ago would have a calculated daily dose of 2 puffs per day. All calculations took under consideration differences in the number of doses between various inhalers.

For the other questions, categorical responses were arranged into pre-set groups and the frequency distribution for responses was compared for differences between compliant and non-compliant patients using a Chi-square test. As defined previously, patient compliance was defined as consuming more than 70% of prescribed anti-inflammatory medication as shown by pharmacy records.

Those questions showing statistical significance in the above analysis were then fitted into a multiple regression model of the form: \( y=\beta_0+\beta_1x_1+\ldots+\beta_5x_5+E_i \), where the model was to predict the coefficients \( \beta_1 \) in such a way as to minimize the residuals. The final regression equation was obtained through examination of p-values of our one way ANOVA and individual t-tests of each possible model.

The questions used in the final regression model were compiled together into a revised questionnaire named the Asthma Compliance Assessment Survey (ACAS) attached in Appendix D. Subsequently, ACAS sensitivity and specificity were calculated as follows:
Gold Standard

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Sensitivity $= \frac{a}{a+c}$  Specificity $= \frac{d}{b+d}$, where

Gold Standard = compliance with anti-inflammatory medication as determined by pharmacy records

New Test = compliance with anti-inflammatory medication as determined by ACAS

+ = non-compliant

- = compliant

Please note that the above calculations of sensitivity and specificity defined positive and negative results based on non-compliance and compliance respectively.
Chapter 3

Results

Patient data were collected for a total of 12 months from November 1998 to August 1999 and May 2000 to July 2000. The results of the study are presented below and are divided into three sections. The first part looks at the patient population on which this research is based. The second section statistically describes the results of the primary objectives mentioned earlier. The final section analyzes the previously described secondary objectives. Please note that the total number of responses for questions may vary because a few patients did not provide answers to some survey questions. Figures and tables are attached in Appendices B and C respectively.

Patient Population

In total 157 patients agreed to participate, but ten were disqualified due to age, diminished mental status, or the use of a nebulizer rather than an MDI. Of the remaining 147 patients, 127 were recruited from the Asthma Centre at the Toronto Western Hospital, while 20 patients were enrolled from the Primary Care Asthma Clinic at Dufferin and St. Clair. As demonstrated by the flowchart in Figure 1, sixty-two participants, termed the missing-data population, were not included in the final analysis either due to incomplete or unavailable pharmacy records. Thirty patients from the missing-data population cited “invasion of privacy” most often as the reason for refusing to give consent for the release of their pharmacy information. For the other 85 patients, comprehensive pharmacy data were extracted and percent compliance was calculated for each patient
as described previously. Percent compliance for these participants was then graphed in a boxplot, for identification of outliers. Eight patients, with a compliance range of 225%-1250%, were eliminated. The remaining 77 patients, which comprised the study or patient population, had a normal distribution of compliance range (approximately 10%-217%) with a mean of 88.4 (standard deviation 49.3). Using the definition of compliance as 70%, 47 patients were deemed compliant, giving this study a compliance rate of 61%.

As mentioned in the introduction different cut-off levels for compliance may be used in other studies. Below is our data reanalyzed using different compliance cut-off levels:

<table>
<thead>
<tr>
<th>Cut-off Level</th>
<th>Compliant</th>
<th>Non-compliant</th>
<th>Compliance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>59</td>
<td>18</td>
<td>77%</td>
</tr>
<tr>
<td>55%</td>
<td>52</td>
<td>25</td>
<td>68%</td>
</tr>
<tr>
<td>60%</td>
<td>48</td>
<td>29</td>
<td>62%</td>
</tr>
<tr>
<td>65%</td>
<td>47</td>
<td>30</td>
<td>61%</td>
</tr>
<tr>
<td>70%</td>
<td>47</td>
<td>30</td>
<td>61%</td>
</tr>
<tr>
<td>75%</td>
<td>46</td>
<td>31</td>
<td>60%</td>
</tr>
<tr>
<td>80%</td>
<td>43</td>
<td>34</td>
<td>56%</td>
</tr>
</tbody>
</table>

As displayed above, it seems that there is a difference of only 2 patients for cut-off levels between 60-75%. Accordingly, using a compliance cut-off level anywhere between 60-75% would not change the major findings of this research. Therefore, it is on this basis that we justify a compliance cut-off level of 70% in this study.
Inhaled therapy used by our study population (n=77) was reported as follows:

**Anti-inflammatory**
- Pulmicort® (budesonide)  n=36
- Flovent® (fluticasone)  n=20
- Becloforte® (beclomethasone)  n=18
- Beclovent® (beclomethasone)  n=3

**Short-acting Bronchodilator**
- Ventolin® (salbutamol)  n=45
- Bricanyl® (terbutaline)  n=8
- Atrovent® (ipratropium)  n=9
- Combivent® (ipratropium+salbutamol)  n=3
- Berotec® (fenoterol)  n=1

NB: Patients who had incomplete records for short-acting bronchodilators were still included in our study population if records for anti-inflammatory medication were available.

**Long-acting Bronchodilator**
- Serevent® (salmeterol)  n=21
- Oxeze® (formoterol fumarate)  n=3

Demographics and asthma characteristics evaluated for the study population are shown in Table 1. There was no significant difference between compliant and non-compliant groups with respect to age, gender, occupation or smoking status. A typical study participant was a 50 year old woman who did not smoke and was either retired or worked in the service industry. The mean asthma duration for this population was 13.4 years, and most had been referred by their family physician to an asthma centre between 1-5 years ago. Again, there was no significant difference between compliant and non-compliant groups with respect to asthma duration, referral to the asthma centre or duration at the asthma centre.
Participants who were recruited for the study, but were excluded from the final analysis due to unavailable pharmacy records, were grouped together into a missing-data population category. As shown in Table 2, this population included those patients for whom consent was obtained but retrieved pharmacy records were incomplete and those who refused to sign the medical release consent form. The typical patient in the missing-data population was a 46.8 years old female non-smoker, who had asthma for approximately 17.2 years. Although there was no statistical difference between the study and missing-data population, patients in the latter group had a higher rate of unemployment, and asthma related hospitalizations. Interestingly, however, there was a significant difference in prescription insurance between the study and missing-data populations. As shown in Figure 2, patients in the study population were statistically more likely to have a drug plan than patients in the missing-data population ($\chi^2=18$, $p<0.05$).

Primary Objectives

RESEARCH QUESTION 1

The aim of this research question was to determine whether a patient's self-reported prescription refill rate predicted his or her compliance. The prescription refill rate was calculated by converting patient responses to question 13 “When was the last time you refilled your prescription?” into puffs per day by dividing the maximum number of doses in a canister by the patient's response. This calculation made the assumption that patients had accurate recall and that all the medication had been consumed during that time period. Responses were collected for both anti-inflammatory and bronchodilator
medication and graphed in a scatter plot against information from pharmacy records. As demonstrated in Figure 3, the number of puffs per day as determined by question 13 correlated significantly with the daily puffs as calculated from pharmacy records for anti-inflammatory medication (n=76, r=0.28, p<0.05). Similarly, responses to question 13 for short-acting bronchodilator showed a statistically significant correlation with pharmacy records as shown in Figure 4 (n=51, r=0.34, p<0.05). Due to its significant correlation, question 13 was further tested as a variable in a multiple regression model in order to assess its capability of predicting compliance.

RESEARCH QUESTION 2

The second research question concentrated on establishing whether a patient’s reported inhaler emptying rate could predict his or her compliance. The inhaler emptying rate was determined by converting answers to question 14 “How long does a canister of your inhaler last?” into puffs per day by dividing the maximum doses in an inhaler by the patient’s answer. As with data from research question 1, responses dealing with both anti-inflammatory and short-acting bronchodilator medication were used with pharmacy records to produce scatter plots. Figure 5 represents responses to question 14 for anti-inflammatory asthma medication, and it illustrates a significant correlation between puffs per day as determined by question 14 and the number of puffs per day as calculated by pharmacy records (n=74, r=0.34, p<0.05). A significant correlation was also found for short-acting bronchodilator medication, as shown in Figure 6 (n=51, r=0.38, p<0.05). In order to test the ability of question 14 to predict patient compliance, it was used in our regression modelling.
RESEARCH QUESTION 3

Determining whether a correlation existed between the assessment of an MDI's level of fullness and patient compliance was the focus of research question 3. About 20% of questionnaire participants had an inhaler with them, which was assessed for canister fullness, using the procedure described in the methods section. Scatter plots for patient compliance as determined by the estimation of canister fullness (puffs/day) and pharmacy records (puffs/day) for anti-inflammatory and short-acting bronchodilator medication are shown in Figure 7 and 8 respectively. Estimation of anti-inflammatory canister fullness correlated with puffs/day as determined by pharmacy records (n=18, r=0.49, p<0.05). The compliance rate for patients whose anti-inflammatory canister was assessed for level of fullness was 50%. Bronchodilator canister assessment was not significant in predicting puffs/day (n=11, r= -0.13, p>0.05), and the compliance rate for patients whose bronchodilator canister was assessed for level of fullness was 55%.

With respect to ensuring reliability of canister fullness estimation, volunteers were selected after completion of the study to estimate the percent fullness for canisters with known fullness. The first 50 trials, performed by the researcher who was involved in this study's canister estimation, produced a Pearson's correlation coefficient of 0.94 (p<0.05) between the actual and estimated canister fullness (Figure 9). The subsequent 50 trials were completed by 5 volunteers each of whom was given 10 trials. Volunteer estimated canister fullness correlated significantly with actual canister fullness for all volunteers combined (Figure 10, 50 trials, r=0.91, p<0.05) as well as individually, where the correlation coefficient range was 0.89-0.98 (p<0.05).
RESEARCH QUESTION 4

Research question 4 looked at a physician's ability to estimate patient compliance. Approximately 50% of clinicians complied with our request for completing a compliance assessment form, which asked the clinician to estimate how many puffs per day of each medication his or her patient was taking. Interestingly, unlike previous studies, we found that clinicians were able to significantly estimate daily medication consumption by his or her patient. As shown in Figure 11, blinded clinician estimates of puffs/day of anti-inflammatory medication statistically correlated with pharmacy record daily consumption (n=16, r=0.41, p<0.05). Figure 12 illustrates that blinded clinicians were also able to estimate daily medication usage with short-acting bronchodilator inhalers (n=13, r=0.32, p<0.05). These physicians who participated were blinded to the purpose of our study. As an additional point of interest, we collected puffs/day estimates from a physician who had extensive knowledge of this study. Interestingly, the unblinded physician was also able to statistically estimate both daily anti-inflammatory consumption (Figure 13, n=18, r=0.34, p<0.05) as well as short-acting bronchodilator consumption (Figure 14, n=13, r=0.68, p<0.05).

RESEARCH QUESTION 5

To inquire into the relationship between a patient's reported MDI inhaler usage and compliance the following three questions were examined:

Question 5 – When was the last time you took your medication?

Question 19 – Everyone forgets to take their medication sometimes. What percent of doses do you estimate you have forgotten?
Question 26 – How often do you take your anti-inflammatory medication?

Patient responses to question 5 were anticipated to be continuous. However, the majority of answers were categorical with patients indicating taking their medication “this morning” or “last night”. Therefore, the data for this question were organized into 2 categories: those who reported taking their medication less than 12 hours ago and those who took it more than 12 hours ago. Patients who indicated that they last took their medication “this morning” or later were taken as having used their inhaler less than 12 hours ago. All others were classified as taking their medication more than 12 hours ago. The data were then analyzed using a chi-square test. The results for short-acting bronchodilator medication, shown in Table 3, demonstrate a significant difference between compliant and non-compliant patients. Please note that compliance was defined as taking more than 70% of prescribed anti-inflammatory medication as determined by pharmacy records. Non-compliant patients were more likely to report short-acting bronchodilator usage within the last 12 hours ($\chi^2 = 6.4$, $p<0.05$). There was no significant difference between compliance groups for reported last use of anti-inflammatory inhalers.

Question 26 looked at medication usage as reported by the patient, while question 19 asked the patient to estimate how often they forgot to take their medication. Because short-acting bronchodilators are usually taken on an as needed basis, only responses for anti-inflammatory medication were examined for the above two questions. Question 26 “How often do you take your anti-inflammatory medication?” reported in puffs/day is plotted against actual usage as determined by pharmacy records in Figure
15. There was a significant correlation between reported anti-inflammatory usage and usage estimated by pharmacy records (n=73, r=0.29, p<0.05). Interestingly, when we adjusted responses to question 26 by the percent of missed doses as reported by the patient in question 19, we found a better correlation (n=73, r=0.32, p<0.05) between “adjusted” puffs per day and pharmacy puffs/day (Figure 16).

Secondary Objectives

RESEARCH QUESTION 6

To examine a difference between compliant and non-compliant patients with respect to experienced problems with using prescribed inhalers, the following questionnaire questions were utilized:

Question 10 “Have you had any problems taking your medication?”

Question 23 “What don’t you like about taking your medication?”

As shown in Figure 17, there was no significant difference between compliant and non-compliant patients when reporting problems with both anti-inflammatory ($\chi^2=0.35$, p>0.05) and short-acting bronchodilator inhalers ($\chi^2=2.7$, p>0.05). Similarly, regardless of compliance status, the same frequency of patients reported something they disliked about their anti-inflammatory medication (Figure 18, $\chi^2=0.43$, p>0.05).
RESEARCH QUESTION 7

The following two questions were used to explore the difference between compliant and non-compliant groups with respect to a patient’s perception of disease severity:

Question 7 “How severe do you feel your asthma is?”

Question 25 “Recently, have you noticed any change in the severity of your asthma?”

Results for question 7, displayed in Figure 19, demonstrate that there is no statistical difference between compliant and non-compliant patients in rating their asthma mild, moderate or severe (χ²=0.63, p>0.05). When asked about any change in their asthma severity, non-compliant patients reported less improvement in their asthma when compared to compliant patients (Figure 20). However, this was not significant (χ²=0.83, p>0.05).

RESEARCH QUESTION 8

The questions used to investigate the difference between groups with respect to financial circumstances were:

Question 12 “What is your opinion on the cost of asthma medication?”

Question 15 “How often do you obtain samples of inhaled medication from your physician?”

Question 16 “Do you have a drug plan?”
In Figure 21, patient responses to question 12 show that opinions on the cost of asthma inhalers did not significantly vary between compliant and non-compliant groups ($\chi^2=1.8$, $p>0.05$). Likewise, patient responses to question 15 did not differ with compliance status (Figure 22, $\chi^2=0.69$, $p>0.05$). Most patients had “never” received samples of medication, while the remainder were given samples either “seldom” or “occasionally”. The results for question 16 were presented earlier as part of the patient population results. While there was no significant difference between the compliant and non-compliant groups with respect to drug insurance, the two groups together were significantly more likely to be insured than those for whom complete pharmacy records were not collected and hence were not included in this final analysis (Figure 2 – refer to Patient Population for results).

RESEARCH QUESTION 9

The difference between compliant and non-compliant groups with respect to a patient’s perception of assistance received in explaining correct inhaler usage was examined using the following questions:

Question 17 “Is your physician helpful in explaining how to use your medication?”

Question 18 “Is your pharmacist helpful in explaining how to use your medication?”

Most patients found both their physician and pharmacist helpful in explaining how to use their puffer as represented by Figure 23 ($\chi^2=0.06$, $p>0.05$) and 24 ($\chi^2=0.002$, $p>0.05$) respectively. There was no difference between compliant and non-compliant group responses.
RESEARCH QUESTION 10

The following questions were used to explore the difference between compliant and non-compliant groups with respect to patient concerns about their condition as well as the perceived impact on quality of life:

Question 22 “Do you have any concerns about having asthma?”

Question 24 “Do you think your asthma affects your quality of life?”

On the whole, non-compliant patients tended to be less concerned about their asthma and reported their asthma to have a smaller impact on their quality of life than compliant patients. Nevertheless, both groups had comparable responses for questions 22 (Figure 25, $\chi^2=2.0$, p>0.05) and 24 (Figure 26, $\chi^2=0.69$, p>0.05).

RESEARCH QUESTION 11

In order to compare the difference for sleep disturbance between compliant and non-compliant groups, the following survey questions were employed:

Question 29 “Do you feel your asthma interferes with your ability to get a good night’s sleep?”

Question 30 “Does your asthma prevents you from sleeping?”

Question 31 “Do you feel well rested in the morning?”

Between 20-40% of survey patients reported a sleep problem associated with their asthma as assessed by question 29 (Figure 27, $\chi^2=0.30$, p>0.05) and 30 (Figure 28, $\chi^2=0.03$, p>0.05). However, there was no difference between compliant and non-
compliant patients. There was also no significant difference for question 31 (Figure 29, \(\chi^2=0.95, p>0.05\)), between compliant and non-compliant patients.

**Regression Model**

Selected questions from our questionnaire, which demonstrated statistically significant results (as presented above) were used as the basis for a multiple regression model. The objective of this model was to predict consumption of anti-inflammatory medication in puffs/day. The following five questions were utilized:

- Question 13 “When was the last time you refilled your prescription for anti-inflammatory medication?” (Q13)
- Question 14 “How long does a canister of your anti-inflammatory inhaler last?” (Q14)
- Question 26 “How often do you take your anti-inflammatory medication?” (Q26)
- Question 19 “How often do you forget to take your anti-inflammatory medication?” (Q19)
- Question 5 “When was the last time you took your short-acting bronchodilator?” (Q5)

Data from the above questions were consolidated and the number of participants was adjusted to 70 due to the fact that not all patients answered every question. A histogram (Figure 30) and normal probability plot (Figure 31) for pharmacy data of these 70 patients, shows that this sample follows a normal distribution with a mean of 3.8 puffs/day as demonstrated by the descriptive statistics in Table 4. A correlation matrix was generated for the above five questions (Q13, Q14, Q26, Q19, Q5) as shown in Table 5. The corresponding scatter plots are shown in Figure 32. Correlations between anti-
inflammatory medication consumption as determined by pharmacy records and questions 14, 26, 19 and 5 were significant (p-value equal to or less than 0.05). Unfortunately question 13 did not correlate significantly with medication consumption as determined by pharmacy records for these 70 patients. Therefore, question 13 was eliminated as a potential predictor of consumption for our model. Other interesting correlations, which were observed include a significant correlation between question 13 and question 14, as well as a significant correlation between question 19 and question 26, among others.

With the elimination of question 13 described above, the remaining four questions were fitted into a multiple regression model. Unfortunately, question 26 did not significantly contribute to our model and hence it was dropped. The other three questions (14, 19, 5) were successfully fitted into a multiple regression model of the form \( y = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k \). Table 6 shows the output for our final regression model, in which the estimated coefficients are as follows: \( \beta_0 = 2.04, \beta_1 = 0.169, \beta_2 = 0.275, \beta_3 = -0.857 \), where

\[ \begin{align*}
\beta_0 &= \text{constant} \\
\beta_1 &= \text{puffs/day as determined by question 14 (Q14)} \\
\beta_2 &= \text{puffs/day adjusted for % forgotten as reported by the patient (Q19)} \\
\beta_3 &= \text{whether the patient used their short-acting bronchodilator more or less than 12 hours ago (Q5)}
\end{align*} \]
The final regression model is provided below:

\[ y = 2.04 + 0.169 (Q14) + 0.275 (Q19) - 0.857 (Q5), \]

where \( y \) represents puffs/day as determined by pharmacy records.

Our null hypothesis stated that Questions 13, 14, 26, 19 and 5 from our original questionnaire would have no effect on predicting daily medication consumption as determined by pharmacy records. Therefore, to test the hypothesis that \( H_0: \beta_i = 0 \), the T-value was computed for each coefficient. All the coefficients were significant (ie. \( \beta_i \) does not equal zero) at the 5% level, except the coefficient of question 5 which was significant at the 10% level as shown in Table 6.

The analysis of variance table for the multiple regression is shown in Table 6. The F statistic for testing the null hypothesis as stated above was 6.01 with a \( p \)-value of 0.001. This means that the regression model as stated by the above equation is statistically significant in predicting puffs/day as determined by pharmacy, thereby rejecting \( H_0 \). The R-squared from Table 6 is 21.5%, which means that 0.215 is the proportion of the variation in puffs/day determined by pharmacy records, that is explained by questions 14, 19 and 5. Examination of residuals is another measure of the "goodness" of the predication made by our model. In this regression, a residual was defined as the difference between the fitted and observed values of daily consumption in puffs/day. The objective of our model consisted of predicting the coefficients \( \beta_i \) in such a way as to minimize the residuals. As shown in Figures 33 and 34 the residuals of this regression model were normally distributed with a zero mean and a finite standard deviation.
Sensitivity and Specificity

The final three questions as described above (Q14 “How long does a canister of your anti-inflammatory inhaler last?”, Q19 “What percent of doses do you estimate you have forgotten?”, Q5 “When was the last time you took your short-acting bronchodilator?”) were put together into a revised questionnaire termed the ACAS as described earlier. Accordingly, the ACAS was then validated for use in a clinical setting through a sensitivity and specificity calculation displayed in Table 7. Estimates of daily anti-inflammatory consumption as determined by our regression model served as the basis for differentiating positive and negative ACAS results. A cut point of 70% was used to define positive and negative results, where a positive result was taken as consuming less than 70% of prescribed anti-inflammatory medication (ie. non-compliant). Similarly, estimates of daily anti-inflammatory consumption as determined by pharmacy records served as the basis for differentiating positive and negative results for our “standard”. A cut point of 70% was used to define positive and negative results, where a positive result was taken as consuming less than 70% of prescribed anti-inflammatory medication (ie. non-compliant). The ACAS had a sensitivity and specificity of 41% and 85% respectively.
Chapter 4

Discussion

This study focused on compiling a set of clinically relevant questions, which could be easily and directly used by a clinician in a medical interview setting to estimate consumption of medication and hence identify non-compliance. While previous research has explored factors affecting non-compliance, as well as strategies to improve adherence, ours is the first study to actually attempt to validate a compliance assessment tool for regular use of inhaled anti-inflammatory medication. The first part of the discussion, which describes general research results, such as our patient population and study design, is followed by discussion of the major, minor and negative results of this study.

Patient Population

Our study population of 77 participants statistically resembled previous research populations in other compliance studies. Braunstein et al. (1996), looked at compliance in a population consisting of 51% female with a mean age of 42, which was similar to our research where a 55% female population, mean age 50, was recruited. Likewise, our study’s average asthma duration of 13.4 years with 46.8% of participants reporting having been hospitalized for their asthma was comparable to Chmelik and Doughty’s (1994) research, where the average asthma duration was 11.1 years with prior asthma-related hospital visits being noted for 55% of the patient population. Moreover, there was no significant difference in demographics and asthma characteristics between our compliant and non-compliant subgroups.
Compliance

Compliance has been defined as “the extent to which a person’s behaviour coincides with medical advice” (Haynes 1979). In this study, compliance was calculated as a percentage of doses taken over doses prescribed with a cut-off level of 70%, above which patients were deemed compliant. Cochrane (1996) argues that compliance cut-off levels seem to be set arbitrarily by researchers, with various studies using levels of between 50-80%. While this may be true, there is no evidence in the literature of a study exploring the relationship between clinical outcome and compliance as was done by Sackett (1976) for anti-hypertensives. Therefore, in order to be as objective as possible a crude average of previous compliance cut-off levels was used in this study. Furthermore, a value of 70% can be justified in this study when one examines the distribution of percent compliance in our sample. As presented earlier, it seems that there is a difference of only 2 patients for cut-off levels between 60-75%. Accordingly, using a compliance cut-off level anywhere between 60-75% would not change the major findings of this research.

Compliance can also be estimated, as described by Chapman et al. (2000), by taking the percent of days on which the proper dosage of medication was taken. This approach was not utilized in this study since pharmacy records do not provide any information on daily medication usage. Instead it provides an estimate of medication consumption over an extended period of time. However, this estimation does not tell us whether a patient who is 50% compliant is taking half of the prescribed medication every day or is consuming the full dose every other day.
In this study population, 47 out of 77 patients were found to be compliant, which is defined as taking at least 70% of prescribed medication. This treatment adherence rate of 61% is within the estimated compliance range of 30-70% as reported in the literature (Spector et al. 1986, Bender et al. 1997, Wamboldt 1998). Our compliance rate is on the upper side of this range, and while it is comparable to treatment adherence of 70% as found by Rand and Wise (1994), it is possible that it may have been inflated for a number of reasons.

First, most of our study participants were drawn from a specialized medical environment where patients were under the care of a respirologist and had regular contact with a nurse educator. Several research studies, such as Peckham et al. (1998) and Edworthy et al. (1999), have found patient education to be beneficial in improving treatment adherence in chronic illness. The fact that the majority of our survey participants had access to educational materials may have contributed to an increased compliance rate in our study. However, it should also be pointed out that the primary care centre from where we recruited the remainder of patients was very much geared to asthma management with books, pamphlets and videos available in the waiting room. Furthermore, there was no significant difference between compliance rates for those under the care of a specialist versus a generalist (primary care physician).

Second, our compliance rate was calculated based on pharmacy records obtained only from our study population. Those patients for whom pharmacy records were unavailable were not included in the compliance rate estimation due to a lack of data (see missing-data population). Therefore, this population may represent a group of
grossly non-adherent patients. With this in mind, by unintentionally excluding non-compliant patients our compliance rate may have been artificially exaggerated.

**Missing-data Population**

As mentioned above, the missing-data population comprises those survey participants for whom pharmacy records were not obtained either due to a lack of consent or an incomplete refill record. In total 62 patients are included in this category subdivided into two groups: no medical release (n=30) and incomplete records (n=32). The lack of consent displayed by the 30 participants who refused to release their pharmacy records, could be due to a desire to conceal non-adherence. However, denied access to prescription information may have come about for other reasons. Patients may be wary of allowing research personnel access to personal information, which may contain data about drugs for other medical conditions. As well, embarrassment over having no prescription coverage or hesitance in revealing the total amount spent on medications may also play a part. Therefore, one cannot conclude that refusal to sign a medical release form is equivalent to poor treatment compliance.

The patients (n=32) who allowed release of their prescription records, but information obtained from the pharmacy was incomplete or unavailable could represent a grossly non-compliant group. But is the lack of pharmacy information sufficient evidence for non-compliance? While it may suggest obvious non-compliance, assuming low adherence in the case of incomplete pharmacy records would be a premature conclusion. Some patients may be getting their medication through samples - four patients actually reported "always" receiving inhaler samples from their physician.
Alternatively, they may be using medication obtained through another family member or a source beyond the pharmacy. For example, one participant reported that as a self-employed individual, prescription inhalers were obtained through a veterinary clinic! However, one finds worrisome trends in this subgroup, suggesting poor asthma control associated with non-adherence. Patients with incomplete pharmacy levels were more likely to be referred for asthma treatment by the emergency department and were more likely to have been hospitalized for their asthma in the past. As well, of all the patients who reported not having a drug plan, 75% were classified as having incomplete pharmacy records. This tendency raises serious issues about the association between the inability to afford medications and non-compliance. While absence of comprehensive drug insurance may not in itself predict non-compliance, it may be an obstacle to achieving adherence.

A related observation is the fact that, while there was no overall statistical difference in demographics or asthma characteristics, the missing-data population was significantly less likely to have medical coverage for prescription drugs than the study population as shown in Figure 2 (p<0.05). This finding is consistent with research completed by Hyland (1998), who suggests that compliance may be negatively influenced by the high cost of asthma medications. Various other studies have proposed that adherence improves with increased income (Spector et al. 1986, Rand et al. 1995, Apter et al. 1998). Greater financial security may help off-set prescription costs and higher paying jobs may be more likely to provide a drug plan. However, Home and Weinman (1999) as well as Hamid et al. (1998) found no relationship between
compliance and socioeconomic status. It is with these conflicting results in mind that the results of this study will have to be appreciated.

The use of pharmacy records as our “gold standard” for adherence measurement has some limitations, which are important to discuss when evaluating the results of this study. As described by Bender et al. (1997), compliance estimates from pharmacy records can be calculated only if the patient’s main source of asthma medication is the pharmacy. This may be problematic since approximately 30% of patients do not fill the prescription in the first place (Levy 1991). Pharmacy records also do not provide any information about actual medication consumption. Patients may be using multiple canisters at the same time and even stock-piling inhalers, leading to an overestimation of compliance (Saunders et al. 1998). As illustrated by Chapman et al. (1998), a confounding factor associated with inhaled medication is poor MDI technique. Since an actuation may not be equivalent to a consumed dose, a patient with an inadequate inhaler technique may not be receiving sufficient medication, even while regularly refilling his/her inhaler.

Although imperfect reflections of actual drug use by patients, pharmacy records were the most feasible standard against which to compare a clinical questionnaire. Such records are widely available for review in a large and relatively unselected population of patients. Pharmacy data were obtained and analyzed as described in Saunders et al. (1998), and results were comparable to other studies which assessed compliance through pharmacy records.
A study by Sherman et al. (2000), which measured compliance using prescription refill rates obtained from the patient's pharmacy, found a compliance rate of 61.4% with 57% of patients eventually being included in the study population. These findings were similar to those in this study, where a compliance rate of 61% was obtained from a study population, comprised of 52.4% of survey participants. As noted above, some participants were not included in the study population due to unattainable pharmacy refill information (see Missing-data Population). Sherman et al. (2000) concluded that prescription refills were an accurate way to identify non-compliance. However, obtaining pharmacy records can be time-consuming and may not be practical in a clinical setting. Therefore, this study focuses on validating easy-to-use questions, which are a direct reflection of medication consumption determined through the use of pharmacy records.

Major Findings

The main finding of this study is a multiple regression model which significantly predicts daily consumption of anti-inflammatory medication. The final regression model is

\[ y = 2.04 + 0.169 \text{ (Q14)} + 0.275 \text{ (Q19)} - 0.857 \text{ (Q5)}, \]

where Q14=question 14, Q19=question 19 and Q5=question 5. This model takes into account intentional non-compliance, inadvertent non-compliance due to forgetfulness as well as increased short-acting bronchodilator usage for poorly controlled asthma as a consequence of non-compliance. For question 14, it makes sense that non-compliant patients would take longer to empty their inhaler, thereby decreasing the estimated puffs/day for these patients as assessed by Q14. Similarly, patients who reported increased percentages of forgetfulness would also have lower estimated puffs/day for Q19. Lower values for both
Q14 and Q19 would all lower the calculated consumption. Question 5 was given a value of 1 or 0, where 1= taking short-acting bronchodilators less than 12 hours ago and 0= taking their short-acting bronchodilators more than 12 hours ago. A zero would in essence eliminate question 5 as a variable in the regression model. However, if a patient took a short-acting bronchodilator less than 12 hours ago, the estimated consumption of this patient would decrease by 0.857 puffs/day! Therefore, for patients taking their short-acting bronchodilator less than 12 hours (presumably because of poor control as a result of non-adherence) a lower consumption estimate would be obtained. Each of the three questions are discussed in further detail below.

Question 14 “how long does a canister of your anti-inflammatory medication last?” explored the relationship between a patient’s reported inhaler emptying rate and compliance. Answers to question 14 were converted to puffs/day by dividing the maximum dose in the inhaler by the patient’s response to question 14. Subsequently, we found a positive correlation between puffs/day as determined by question 14 and puffs/day as determined by pharmacy records as shown in Figure 5. Question 14 was included in our final regression model with a coefficient of 0.169.

A main source of variation in responses to question 14 is the fact that the question required patients to estimate their own pattern of medication usage. For example, question 14 asked a patient how long a canister of their anti-inflammatory medication lasts. This is not something a patient keeps track of regularly, and so he or she would have to depend on his or her own memory and/or capability to estimate time in order to answer this question. These patient responses, therefore, are susceptible to inter-subject
variability. Is one person better at estimating time than another? This is indeed a possibility. Having said this, however, our biggest weakness could, in fact, be our greatest strength. Because our questions explore issues which patients do not encounter often, these “estimated” responses may better predict medication consumption. In other words, patients who are frequently reminded to take their medication “2 puffs twice daily” would likely report that they are taking 4 puffs/day. Since patients are not usually informed that their inhaler will only last 30 days, a patient would have to estimate this value without relying on previously obtained information. Along the same lines, question 14 could be limited by the number of times it could be asked of a patient. Meaning that over time, patients may "learn" the "correct" response to question 14, thereby decreasing its usefulness in estimating daily consumption.

Question 19 “What percentage of doses do you estimate you have forgotten?”, a subset of research question 5, is also included in our regression model with a coefficient of 0.275. Values used in the regression for question 19 were obtained in the following manner: The number of forgotten doses (calculated from percent of doses forgotten) were subtracted from patient responses in question 26 (the patient’s reported daily consumption) to obtain an adjusted puffs/day estimate for question 19. Therefore, question 19 (adjusted) is simply a proportion of question 26 and it correlates better with pharmacy estimated puffs/day than question 26 alone. Additionally, question 19 adopts an open-ended approach for communicating with a patient. Instead of asking the patient “do you forget to take your medication?”, which is a closed-ended question producing a "yes" or "no" answer, question 19 invites a more candid response.
Good communication, and the use of open-ended questioning have been endorsed by numerous studies (Steele et al. 1990, Geppert and Collazo 1998, Mellins et al. 2000). By asking the patient to estimate the percent of doses he or she forgets, one is already assuming that the patient does indeed forget. Especially when preceded by a statement such as "everyone forgets to take their medication" (as done in this study), a patient can be put at ease about the fact that they do indeed forget to take their medication. As shown by our regression equation, question 19 can be very useful in predicting consumption.

Research question 5, explored reported medication usage for short-acting bronchodilator. A significant correlation between time elapsed since the last reported use of a short-acting bronchodilator and compliance with inhaled anti-inflammatory therapy was found (Table 3, p<0.05). Participants deemed compliant by pharmacy records were more likely to have taken a short-acting bronchodilator more than 12 hours ago, while non-compliant participants reported taking their rescue medication less than 12 hours ago. According to the Canadian Asthma Consensus Guidelines, use of a short-acting bronchodilator more than three times a week indicates poor asthma control and the need for inhaled corticosteroid therapy (Boulet et al. 1999). Non-adherence to a treatment regimen can be a cause for poor asthma control, which in turn can result in fatal or near-fatal exacerbations. A case-control study by Turner et al. (1998) found that patients experiencing a near-fatal asthma episode used higher doses of β2-agonists than controls and had a compliance rate of only 29%. The link between near-fatal asthma and β2-agonist overuse has also been found in other studies (Spitzer et al. 1992, Burgess et al.
1994). Additionally, it has been speculated that chronic overuse of β2-agonists may lead to a worsening of asthma severity (Sears et al. 1990, Spitzer et al. 1992). An interesting study by Diette et al. (1999) found that the lack of access to asthma medication was a risk factor for β2-agonist overuse. If one infers that impaired access to asthma inhalers can be influenced by the lack of drug coverage, then the issue discussed earlier regarding low income as an obstacle to compliance is emphasized.

A patient who frequently uses a short-acting bronchodilator to relieve asthma symptoms may have poorly controlled asthma as a consequence of non-adherence. Such a patient, especially one who also does not have medical coverage for prescription drugs, should be a signal for exploring issues affecting compliance. Inquiring into a patient’s use of β2-agonists can offer insight to a physician attempting to estimate compliance. This fact is reinforced by our regression model, where the coefficient for question 5, time elapsed since last used short-acting bronchodilator, is negative 0.857. This would lower estimated consumption, suggesting that patients who use their short-acting bronchodilators more frequently, consume less anti-inflammatory medication. This brings us back to the point made earlier that patients who overuse their short-acting bronchodilator may be experiencing poorly controlled asthma as a consequence of low compliance with anti-inflammatory medication.

The three main questions (14, 19 and 5) discussed above were compiled into the Asthmatic Compliance Assessment Survey (ACAS – in Appendix D). Validity of the ACAS was assessed through a calculation of sensitivity and specificity by a method described earlier. In this study the target condition of interest was non-compliance, hence
a positive result represented the presence of non-compliance while a negative result represented the absence of non-compliance (or the presence of compliance). As shown in Table 7, sensitivity and specificity of the ACAS was 41% and 85% respectively.

Sensitivity measures the ability of a test to recognize those individuals who are positive for a certain variable. In terms of non-compliance (positive result), a high sensitivity would mean that an individual who is deemed compliant (negative test result) by the questionnaire is likely to be compliant. On the other hand, specificity measures the ability of a test to accurately detect those individuals who are negative for a test variable. Therefore, a measure with a high specificity would indicate that non-compliance is likely in a person that is suggested to be non-compliant (positive test result) by that measure. Clinically, this means that a highly sensitive test would have few false negatives, while a test with a high specificity would have few false positives. In this way a highly sensitive test with a negative result rules out the presence of the condition (non-compliance) and a highly specific test with a positive result rules in the presence of the condition (non-compliance). With respect to this study's goal of designing a tool for assessing non-compliance, the ACAS has a good specificity (85%), which means that patients testing "positive" on the ACAS (reflecting non-compliance) are likely to be truly non-compliant. However, ACAS has a low sensitivity (41%) and this hinders it as a clinical tool since non-compliance cannot be confidently ruled out on patients testing "negative" on the ACAS.
Minor Findings

One disappointing result in this study was the absence of question 13 from our regression equation. This finding is in direct contrast to our hypothesis in which we predicted that inquiring about a patient’s inhaler refill rate would improve detection of non-compliance. While discouraging, there may be a convincing explanation for this finding. Question 13 asks “when was the last time you refilled your prescription for your anti-inflammatory medication?” and the response provided was then converted into puffs per day by dividing the maximum number of doses in the inhaler by the patient’s response to question 13. However, there is one flaw in this calculation - it is assumed that the patient completely consumed all the doses contained within the canister since they last reported refilling their inhaler. This, of course, may not be a perfectly correct assumption to make since the patient may have only recently refilled his or her prescription, leading to an overestimate of consumption. Such an overestimation would lead to a large discrepancy between puffs/day as determined by question 13 and puffs/day as determined by pharmacy records, and hence affect the ability of question 13 to correlate with pharmacy record consumption. This is suggested by the fact that question 13 has the largest standard deviation and maximum value out of all variables fitted for our regression model (Table 4). This possible explanation is further supported by looking at the correlation matrix in Table 5. Table 5 shows a significant correlation between question 13 and question 14 \((r=0.46, p<0.05)\). This relationship reflects the fact that responses to question 13 and 14 were similar and hence responses to question 13 are represented indirectly in our regression model through question 14. Perhaps by rephrasing the question in terms
of "how often" rather than "when" a patient refilled their prescription, error would be reduced and a better estimate of medication consumption obtained.

A subset of research question 5, questioned patients how frequently they used their medication. Figure 15 illustrates patient responses to question 26, "How often do you take your medication?", which significantly correlated with pharmacy data. This finding is inconsistent with past studies, showing that patients do not accurately report medication usage to their physicians, often exaggerating ICS consumption and under-reporting bronchodilator usage (Spector et al. 1986, Rand et al. 1992, Yeung et al. 1994, Cochrane 1996). Our contradictory result could be an artifact of the following factors. Basically, these data were collected by research personnel, not the patient's own physician, and patients were blinded to the purpose of the study, hence they may have provided more accurate responses about their medication usage. As well, inquiry into inhaler medication usage was posed in an open-ended way, thereby generating better communication and consequently responses that may have been more accurate. Prior research has suggested that an open-ended method of interview has a better outcome with compliance estimation (Geppert and Collazo 1998). Alternatively, these results could simply be a reflection of our high-end compliance rate.

Even though question 26 was significantly correlated with puffs/day as determined by pharmacy records, it is not included in our final regression model. The reasoning for this may be as follows. According to the correlation matrix in Table 5, question 26 is highly correlated with question 19 (r=0.98, p<0.05). Question 19 asked patients to estimate the percentage of doses they had forgotten to take. This percentage
of forgotten doses was taken away from patient responses in question 26 to obtain a puffs/day value for question 19. Therefore, in essence, question 19 is simply a proportion of question 26 and so patient responses to question 26 are already represented in our regression equation through question 19.

Research question 3, which compared canister fullness estimated by research personnel to pharmacy records, found a significant relationship for anti-inflammatory medication (n= 18, r=0.48, p<0.05). These results, however, should be viewed cautiously in view of the fact that only 20% of study participants had canisters available for assessment. There are also a few limitations of using canister estimation. First of all, if an inhaler has been recently refilled or is found to be 100% full, then the formula, which was used to calculate compliance, is not accurate. Similarly, if a patient refills multiple canisters at once, it is virtually impossible to determine their compliance, since it is not known whether they are using their inhalers consecutively or concurrently and whether they have brought their 1st, 2nd or 3rd canister. This is actually a plausible explanation for why our bronchodilator canister assessment results were not significant. Patients may be more inclined to have multiple "rescue" inhalers in several places, and this, as discussed above, would affect our calculation.

As with pharmacy records, canister fullness estimation provides neither information about actual medication consumption nor information about whether proper inhaler technique was used. Another problem reported in using canisters to estimate compliance is the "dumping" phenomenon. Previous studies, using electronic actuation monitors, have shown that some patients empty their canisters all at once in an attempt
to appear compliant (Schemier and Leidy 1998, Hamid et al. 1998). Taking this into account, the design of this study arranged for a canister to be examined in such a way that the participants did not know that compliance was being estimated (subjective estimation rather than objective measurement). Prior research has shown that adherence changes when patients know that their compliance is being monitored (Yeung et al. 1994, Cochrane 1995, Simmons et al. 1996). As well, the fact that patients were not informed ahead of time that their canister was going to be examined made it unlikely that they would have “dumped” their inhalers up front. Nonetheless, dumping may still be legitimate concern in the application of this study. If canister fullness estimation is used on a regular basis as a measurement of compliance, patient awareness may increase and as a result so could inhaler dumping.

Another point that should be addressed is the fact that the researcher who performed all the canister estimations was not blinded to the purpose of the study. Hence, the estimation may have been influenced by responses made by the patient during the interview. In order to assess the reliability with which canister fullness is estimated, the researcher was subjected to 50 blind trials with canisters of known fullness. The researcher’s estimates strongly correlated with the actual canister fullness (r=0.94, p<0.05). To look at the reproducibility of these results, 5 volunteers (2 clinicians, 1 asthma nurse educator, 1 researcher, 1 medical student) were subjected to 10 trials each. The combined 50 trials between them produced a correlation of 0.91 (p<0.05) with an individual range of 0.89-0.98. These are indeed interesting results, which suggest that
canister fullness estimation is a learnable skill, especially with increased practice as shown by the correlation of r=0.98 achieved by the nurse educator.

Research question 4, which explored the relationship between physician estimation of adherence and pharmacy records, found that blinded physicians estimates of medication consumption for both anti-inflammatory and bronchodilator medication correlated with daily consumption as estimated by pharmacy records (Figure 11 and 12). This finding is not consistent with prior research, which reported that physicians were no better than chance in compliance assessment (Caron and Roth 1968, Mushlin and Appel 1977, Sherman et al. 2000). An explanation for this phenomenon can be found by scrutinizing our clinician compliance assessment form. Medication consumption as reported by the patient (question 26) was recorded on the assessment form and the clinician was instructed to record his or her own estimate of consumption. The flaw in the assessment form rests with the fact that the patient’s medication consumption was already indicated. Since the clinician knew what the patient had reported, simply entering a value similar to the patient’s would in fact almost guarantee an accurate estimation. This is due to the fact that question 26 (the patient’s estimate of daily consumption) correlated significantly with daily consumption as determined by pharmacy records. Additionally, due to the fact that only half of the assessment forms were filled out, it is possible that the clinicians who complied with our request were the ones who were skilled in compliance estimation and hence this could account for the significance of our results. Furthermore, the fact that this study had an above average compliance rate to 61%, may also have assisted clinician estimates in becoming significantly correlated with
pharmacy record puffs/day. The above analysis can also be used to explain similar significant results obtained by our unblinded clinician (Figure 13 and 14).

**Negative Findings**

There were no statistically significant findings for research questions 6 through 11. This study found no reported difference in difficulty using an inhaler between compliance groups. As well, reported dissatisfaction with his or her medication, concerns about side effects and negative impact on quality of life had no effect on a patient’s compliance. These results contradict our original hypothesis in which we predicted that medication dislikes and difficulty using inhalers would lower adherence. This assumption was based on work carried out by Home and Weinman (1999), who found that compliance varied inversely with concerns and van der Palen et al. (1997), who reported that patients were reluctant to use ICS regularly. Despite the findings in these studies, our inaccurate prediction may be due to multifactorial behavior effects. For example, the presence of an aversive side effect could be a possible reason for noncompliance or it could simply be an indication that the patient is taking his/her medication regularly enough to notice adverse effects. On the contrary, the absence of a problem could either enhance compliance or be an indication of no regular usage by a non-compliant patient.

With respect to reported disease severity, our study found no difference between compliance groups for this variable. Numerous other studies have also found no effect of disease severity on adherence (Mann et al. 1992, Apter et al. 1994). This expected result demonstrates the complexity of this variable. Mix in a patient’s subjective perception of disease severity with the reversible nature of asthma as well as questionable inhaler
the technique and one can see why it would be quite difficult to isolate the impact of disease severity on compliance.

The results for research question 8, which investigated the difference between compliance groups with respect to financial circumstances were mixed. There was no statistical difference between compliance groups for a patient's opinion on the expense associated with purchasing inhalers, frequency of obtaining sample medication, or access to drug insurance. However, there was a significant difference in prescription coverage between our study and missing-data population discussed earlier (see Missing-data Population). While prior research has suggested no association between adherence and income (Hamid et al. 1998, Home and Weinman 1999), a conclusion that finances do not impact compliance would be premature. Hyland (1998) suggested that high medication costs can hinder compliance and Diette et al. (1999) found that difficulty in obtaining asthma medication can result in β-agonist overuse.

Based on previous research, we anticipated observing a significant difference between compliance groups for assistance offered by the patient's physician or pharmacist. Good communication has been suggested as a compliance enhancing strategy (Bone 1996, Geppert and Collazo 1998, Mellins et al. 2000). Most patients reported that they found their doctor or pharmacist to be a valuable source of information. While this response distribution may be true, it could be also a biased finding reflecting the patient's wish to please the healthcare provider or due to the fact that patients have low expectations of their health care provider.
Research question 11, which investigated any difference between compliance groups with respect to sleep disturbance did not produce any significant conclusions. Between one third and one quarter of survey participants reported a sleep disturbance. This is a much lower incidence than reported by Storms et al, whose 1994 and 1996 studies noted nocturnal symptoms in 67% and 59% of asthmatics respectively. Our lower estimate of sleep disturbance could be due to the fact that our compliance rate was in the upper range of values reported in the literature.

Further Research

Our study provides some insightful findings into the development of a compliance estimation instrument. However, these preliminary findings which identified 3 key questions as described in the ACAS should be followed up with further investigations to look at the potential application of our assessment tool through a prospective study. It would be especially useful to observe the performance of the ACAS in a real clinic setting, where a physician would administer the questionnaire instead of a researcher unrelated to the patient's medical care. Would physicians be better able to predict non-adherence with help from ACAS? Furthermore, looking at whether our questions are applicable in long-term patient compliance assessment, rather than just once as done in this study, would also be beneficial. Would patients learn the "correct" responses over time?
Conclusion

Compliance with anti-asthma medication is essential in controlling respiratory symptoms and exacerbation in asthma patients. Unfortunately, not all patients adhere to their treatment regimen and it is difficult for physicians to evaluate a patient's compliance, since there is no simple and accurate method currently available to assist in its assessment. Our study evaluated the clinical effectiveness of using interview based questions for predicting medication consumption and hence compliance. Patient responses to the questionnaire were gathered and compared to puffs/day, as calculated by pharmacy records, which served as our gold standard for adherence assessment in this study. Questions, which asked patients how long their inhaler lasts (Q14), the percent of doses they forget (Q19) and how long ago they used their β2-agonist (Q5), were found to have a significant correlation with pharmacy records. These questions were then fitted into multiple regression model to produce the following equation: \[ y = 2.04 + 0.169 \times (Q14) + 0.275 \times (Q19) - 0.857 \times (Q5). \] Clinical usefulness of this model was evaluated through ACAS (a revised questionnaire containing Q14, Q19 and Q5), which had a sensitivity and specificity of 41% and 85%. Such a result indicates that the ACAS is likely to be correct when it identifies non-compliant individuals (positive test result). However, it is not as likely that the ACAS will correctly identify individuals as being compliant (negative test result), thereby decreasing the ability of this test to detect non-compliance which was the original objective of this study.
References


Geppert, EF and S Collazo. Establishing a Partnership with the Patient with Asthma. Journal of Allergy and Clinical Immunology 1998.101:S405-S408.


Consent Form

ATTITUDES TOWARD ASTHMA SURVEY
CONSENT FORM

I have been asked to take part in survey assessing patient attitudes towards asthma and its treatment. I will be asked a few questions about how I perceive my asthma and it should take about ten minutes to complete.

This survey is for research purposes only. All information gathered is totally anonymous and will be kept completely confidential. My physician and members of the physician's staff will not be told of my responses to any of these questions. All information gathered will be used to make group statistics only and if a publication arises from this study, only group results will be used. I am free to withdraw my participation at any time. This survey will in no way affect my medical treatment. This study is affiliated with the University of Toronto and with Dr. Chapman at the Toronto Western Hospital's Asthma Centre.

I have been given the opportunity to ask any questions I may have about this survey.

I have read and understood the above.

________________________________________________________________________
First Name (please print)   Last Name (please print)

________________________________________________________________________
Signature                  Date

________________________________________________________________________
Witness
# Asthma Survey

**ASTHMA SURVEY**

1) Last Name: ____________________________
   
   First Name: ____________________________
   
   Occupation: ____________________________
   
2) Age: ____________ 3) Gender: ____________
   
4) What medications are currently prescribed for you?
   
   **Anti-inflammatory:**
   
   1. ____________________________
   
   2. ____________________________
   
   3. ____________________________
   
   **Bronchodilator:**
   
   1. ____________________________
   
   2. ____________________________
   
   3. ____________________________
   
5) When was the last time you took your medication?
   
   **Anti-inflammatory:**
   
   1. ____________________________
   
   2. ____________________________
   
   3. ____________________________
   
   **Bronchodilator:**
   
   1. ____________________________
   
   2. ____________________________
   
   3. ____________________________
   
6) When were you first diagnosed with asthma?
   
   ____________________________
   
7) How severe do you think your asthma is?
   
   mild: _______ moderate: _______ severe: _______
   
8) How long have you been coming to the Asthma Centre?
   
   ____________________________
   
9) Who referred you to the Asthma Centre?
   
   ____________________________
10) Have you had any problems taking your medication?

Anti-inflammatory:  Bronchodilator:
Yes:  No: Yes:  No:

11) Have you ever been hospitalized for your asthma?

Yes:  No:

12) What is your opinion on the cost of asthma medication?

Very expensive:  Expensive:  Ok:  Don't know:

13) When was the last time you refilled your prescription?

Anti-inflammatory:  Bronchodilator:
1.  1.  
2.  2.  
3.  3.  

14) How long does a canister of your inhaler last?

Anti-inflammatory:  Bronchodilator:
1.  1.  
2.  2.  
3.  3.  

15) How often do you obtain samples of inhaled medication from your physician?

Never:  Seldom:  Occasionally:  Always:

16) Do you have a drug plan?

Yes:  No:

17) Is your physician helpful in explaining how to use your medication?

Yes:  No:

18) Is your pharmacist helpful in explaining how to use your medication?

Yes:  No:
19) Everyone forgets to take their medication sometimes. What percent of doses do you estimate you have forgotten?

__________________________________________________________

20) What do you like about the Asthma Centre?

__________________________________________________________

__________________________________________________________

21) What don't you like about the Asthma Centre?

__________________________________________________________

__________________________________________________________

22) Do you have any concerns about having asthma?

    Yes: ______   No: ______

23) What don't you like about taking your medication?

__________________________________________________________

__________________________________________________________

24) Do you think your asthma affects your quality of life?

    Yes: ______   No: ______

25) Recently have you noticed any change in the severity of your asthma?

    Improved: ______   Same: ______   Worse: ______

26) How often do you take your medication?

    Anti-inflammatory:

        1. __________________________
        2. __________________________
        3. __________________________

    Bronchodilator:

        1. __________________________
        2. __________________________
        3. __________________________

27) Have you been personally affected by recent health cut-backs?

    Yes: ______   No: ______
28) Are you a smoker or non-smoker?
   Smoker: _________  Non-smoker: _________

29) Do you feel that your asthma interferes with your ability to get a good night's sleep?
   Yes _________  No _________

30) Does your asthma prevent you from sleeping?
   Yes _________  No _________

31) Do you feel well rested in the morning?
   Yes _________  No _________

Canister Assessment:
Medical Release Form

RELEASE OF MEDICAL INFORMATION REQUEST

Thank you for participating in the asthma survey. Your co-operation was greatly appreciated.

In order to accurately analyze the results of this survey we will require additional information about your medication not provided by this survey. We would like your permission to contact your pharmacy about your asthma medication.

This is an optional part of the study, and will not affect your treatment in any way. All information collected will be kept confidential and will be used only within the scope of this study.

Please do not hesitate to ask any questions and feel free to withdraw your participation at any time.

Thank you.
RELEASE OF MEDICAL INFORMATION

This request is optional and all information will be kept confidential.

Patient's full name: ________________________________

Date of Birth: ________________ Phone: ______________________

Address: ____________________________________________

____________________________________________________

Request for: Pharmacy Records: ______________

Pharmacy Address: ______________________________________

____________________________________________________

Phone: ______________________ Fax: ______________________

I authorize the release of the above information to:
  Katherine Walewski
  c/o Dr. Kenneth Chapman, MD, MSc., FRCP(C), FACP
  Director - Asthma Centre
  The Toronto Hospital - Western Division
  399 Bathurst Street 4-011 E.C.W.
  Toronto, Ontario M5T 2S8

Patient's Name: ______________________________________
(Please Print)

Signature: ____________________________________________

Date: ______________________________________________

Witness: ____________________________________________
Physician Assessment Form

ATTITUDES TOWARDS ASTHMA SURVEY

Patient Name: ____________________________________________

According to the patient, s/he is currently on:

1. ____________________  ____________ puffs per day per week
2. ____________________  ____________ puffs per day per week
3. ____________________  ____________ puffs per day per week
4. ____________________  ____________ puffs per day per week
5. ____________________  ____________ puffs per day per week

Please indicate your estimate of the amount of medication consumed by this patient below:

1. ____________________  ____________ puffs per day per week
2. ____________________  ____________ puffs per day per week
3. ____________________  ____________ puffs per day per week
4. ____________________  ____________ puffs per day per week
5. ____________________  ____________ puffs per day per week

Thank you.
APPENDIX B
Figure 1

157 patients

Survey Consent form signed?

Yes

147 patients

No

10 patients

Pharmacy Release Consent Given?

Yes

117 patients

No

30 patients

Pharmacy Records Complete?

Yes

85 patients

No

32 patients

Conform to normal distribution?

Yes

77 patients

No

8 patients

Are they more than 70% compliant?

Yes

47 patients

No

30 patients
Figure 2

Frequency distribution for responses for "Do you have a drug plan?"

PROPORTION OF SUBJECTS

HAVE A DRUG PLAN?

Incomplete Records □ No Incomplete Release □ No medical Release □ Non-compliant □ Compliant
Figure 3 (n=76, r=0.28)

RELATIONSHIP BETWEEN PUFFS/DAY AS DETERMINED BY QUESTION 13 "WHEN WAS THE LAST TIME YOU REFILLED YOUR PRESCRIPTION FOR ANTI-INFLAMMATORY MEDICATION?" AND PUFFS/DAY AS DETERMINED BY PHARMACY RECORDS

Figure 4 (n=51, r=0.34)

RELATIONSHIP BETWEEN PUFFS/DAY AS DETERMINED BY QUESTION 13 "WHEN WAS THE LAST TIME YOU REFILLED YOUR PRESCRIPTION FOR SHORT-ACTING BRONCHODILATOR MEDICATION?" AND PUFFS/DAY AS DETERMINED BY PHARMACY RECORDS
Figure 6 (n=74, r=0.34)

RELATIONSHIP BETWEEN PUFS/DAY AS DETERMINED BY QUESTION 14 "HOW LONG DOES A CANISTER OF YOUR ANTI-INFLAMMATORY INHALER LAST?" AND PUFS/DAY AS DETERMINED BY PHARMACY RECORDS

Figure 6 (n=51, r=0.38)

RELATIONSHIP BETWEEN PUFS/DAY AS DETERMINED BY QUESTION 14 "HOW LONG DOES A CANISTER OF YOUR SHORT-ACTING BRONCHODILATOR LAST?" AND PUFS/DAY AS DETERMINED BY PHARMACY RECORDS
Figure 9 (r=0.94)

VOLUNTEER ESTIMATED CANISTER FULLNESS VERSUS ACTUAL CANISTER FULLNESS

Figure 10 (r=0.91)

VOLUNTEER (n=5) ESTIMATED CANISTER FULLNESS VERSUS ACTUAL CANISTER FULLNESS
Figure 11 (n=16, r=0.41)

RELATIONSHIP BETWEEN PUFFS/DAY AS DETERMINED BY BLINDED CLINICIANS (n=5) AND PUFFS/DAY AS DETERMINED BY PHARMACY RECORDS FOR ANTI-INFLAMMATORY MEDICATION

Figure 12 (n=13, r=0.32)

RELATIONSHIP BETWEEN PUFFS/DAY AS DETERMINED BY BLINDED CLINICIANS (n=5) AND PUFFS/DAY AS DETERMINED BY PHARMACY RECORDS FOR SHORT-ACTING BRONCHODILATOR
BUCCAL MUCOSA TISSUE HISTOLOGY

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*Note: Data collected from 10 volunteers.*

**Figure 14** (n=10, r=0.68)
Figure 15 (n=73, r=0.29)

RELATIONSHIP BETWEEN PUFFS/DAY AS DETERMINED BY QUESTION 26 "HOW OFTEN DO YOU TAKE YOUR ANTI-INFLAMMATORY MEDICATION?" AND PUFFS/DAY AS DETERMINED BY PHARMACY RECORDS

Figure 16 (n=73, r=0.32)

RELATIONSHIP BETWEEN PUFFS/DAY AS DETERMINED BY QUESTION 19 "WHAT PERCENTAGE OF DOSES DO YOU ESTIMATE YOU HAVE FORGOTTEN?" AND PUFFS/DAY AS DETERMINED BY PHARMACY RECORDS
Figure 17
FREQUENCY DISTRIBUTION FOR RESPONSES TO "HAVE YOU HAD ANY PROBLEMS TAKING YOUR MEDICATION?"

Figure 18
FREQUENCY DISTRIBUTION FOR RESPONSES TO "WHAT DO YOU NOT LIKE ABOUT TAKING YOUR MEDICATION?"
Figure 19
FREQUENCY DISTRIBUTION FOR RESPONSES TO "HOW SEVERE DO YOU FEEL YOUR ASTHMA IS?"

Figure 20
FREQUENCY DISTRIBUTION FOR RESPONSES TO "RECENTLY, HAVE YOU NOTICED ANY CHANGE IN THE SEVERITY OF YOUR ASTHMA?"
Figure 21

FREQUENCY DISTRIBUTION FOR RESPONSES TO "WHAT IS YOUR OPINION ON THE COST OF ASTHMA MEDICATION?"

![Bar chart showing frequency distribution for responses to the cost of asthma medication.]

- Very Exp
- Expensive
- Ok
- Don't know

Compliant: ■
Non-compliant: □

Figure 22

FREQUENCY DISTRIBUTION FOR RESPONSES TO "HOW OFTEN DO YOU OBTAIN SAMPLES OF INHALED MEDICATION FROM YOUR PHYSICIAN?"

![Bar chart showing frequency distribution for responses to how often obtaining samples of inhaled medication.]

- Never
- Seldom
- Occasion
- Always

Compliant: ■
Non-compliant: □
Figure 23

FREQUENCY DISTRIBUTION FOR RESPONSES TO "IS YOUR PHYSICIAN HELPFUL IN EXPLAINING HOW TO USE YOUR MEDICATION?"

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<tbody>
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<td>Non-compliant</td>
</tr>
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</table>

Figure 24

FREQUENCY DISTRIBUTION FOR RESPONSES TO "IS YOUR PHARMACIST HELPFUL IN EXPLAINING HOW TO USE YOUR MEDICATION?"

<table>
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<th>Yes</th>
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<tbody>
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<td>Non-compliant</td>
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Figure 25
FREQUENCY DISTRIBUTION FOR RESPONSES TO "DO YOU HAVE CONCERNS ABOUT HAVING ASTHMA?"

![Frequency distribution chart for concerns about having asthma.]

Figure 26
FREQUENCY DISTRIBUTION FOR RESPONSES TO "DO YOU THINK YOUR ASTHMA AFFECTS YOUR QUALITY OF LIFE?"

![Frequency distribution chart for asthma's impact on quality of life.]

Compliant
Non-compliant

PROPORTION OF SUBJECTS

Yes
No

Yes
No
Figure 27
FREQUENCY DISTRIBUTION FOR RESPONSES TO "DO YOU FEEL YOUR ASTHMA INTERFERES WITH YOUR ABILITY TO GET A GOOD NIGHT'S SLEEP?"

Figure 28
FREQUENCY DISTRIBUTION FOR RESPONSES TO "DOES YOUR ASTHMA PREVENT YOU FROM SLEEPING?"

Figure 29
FREQUENCY DISTRIBUTION FOR RESPONSES TO "DO YOU FEEL WELL RESTED IN THE MORNING?"
Figure 30

[Histogram showing frequency distribution of pharmacy puffs per day]
Figure 31

Normal Probability Plot for PHARMACY

ML Estimates
Mean: 3.75575
StDev: 2.15492
### Figure 32

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</tr>
<tr>
<td>0.25</td>
<td></td>
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<td></td>
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</table>

<table>
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<th>2.69023</th>
<th>7.24595</th>
<th>7.0833</th>
<th>20.1389</th>
<th>10.1389</th>
<th>3.7500</th>
<th>9.5</th>
<th>4.5</th>
<th>7.69</th>
<th>3.39</th>
<th>0.75</th>
<th>0.25</th>
</tr>
</thead>
</table>


Figure 33

Residuals Versus the Fitted Values
(response is Pharmacy)
Figure 34

Normal Probability Plot of the Residuals
(response is PHARMACY)
### TABLE 1
**STUDY POPULATION CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Compliant (n=47)</th>
<th>Non-compliant (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yrs)</td>
<td>50.9 +/- 17.8</td>
<td>48.7 +/- 17.3</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>55.3</td>
<td>53.3</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>14.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Occupation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>8.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Services</td>
<td>21.3</td>
<td>37.5</td>
</tr>
<tr>
<td>Manual</td>
<td>12.7</td>
<td>15.7</td>
</tr>
<tr>
<td>Professional</td>
<td>8.5</td>
<td>0</td>
</tr>
<tr>
<td>Student</td>
<td>8.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Retired</td>
<td>31.9</td>
<td>28.1</td>
</tr>
<tr>
<td>Other/NA</td>
<td>8.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Mean Asthma Duration (yrs)</td>
<td>11.6 +/- 9.0</td>
<td>16.1 +/- 15.7</td>
</tr>
<tr>
<td>Time at Asthma Centre (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>17.0</td>
<td>13.8</td>
</tr>
<tr>
<td>1-12 months</td>
<td>19.1</td>
<td>13.8</td>
</tr>
<tr>
<td>1-5 years</td>
<td>48.9</td>
<td>41.4</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>14.9</td>
<td>31</td>
</tr>
<tr>
<td>Referral to Asthma Centre (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalist</td>
<td>36.2</td>
<td>55.2</td>
</tr>
<tr>
<td>Specialist</td>
<td>27.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Clinic/ER</td>
<td>8.5</td>
<td>20.7</td>
</tr>
<tr>
<td>Other</td>
<td>27.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Prior Hospital Admission (%)</td>
<td>42.5</td>
<td>53.3</td>
</tr>
</tbody>
</table>

### TABLE 2
**MISSING DATA POPULATION CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No release (n=30)</th>
<th>Incomplete records (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yrs)</td>
<td>48.1 +/- 12.6</td>
<td>45.5 +/- 18.6</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>63.3</td>
<td>53.1</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>10</td>
<td>21.9</td>
</tr>
<tr>
<td>Occupation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>10.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Services</td>
<td>36.7</td>
<td>43.6</td>
</tr>
<tr>
<td>Manual</td>
<td>23.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Professional</td>
<td>10</td>
<td>3.1</td>
</tr>
<tr>
<td>Student</td>
<td>3.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Retired</td>
<td>13.3</td>
<td>18.8</td>
</tr>
<tr>
<td>Other/NA</td>
<td>3.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Mean Asthma Duration (yrs)</td>
<td>15.9 +/- 15.1</td>
<td>18.5 +/- 15.8</td>
</tr>
<tr>
<td>Time at Asthma Centre (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>26.7</td>
<td>31.3</td>
</tr>
<tr>
<td>1-12 months</td>
<td>6.7</td>
<td>18.8</td>
</tr>
<tr>
<td>1-5 years</td>
<td>36.7</td>
<td>28.1</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>30</td>
<td>21.9</td>
</tr>
<tr>
<td>Referral to Asthma Centre (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalist</td>
<td>16.7</td>
<td>54.8</td>
</tr>
<tr>
<td>Specialist</td>
<td>20</td>
<td>3.2</td>
</tr>
<tr>
<td>Clinic/ER</td>
<td>23.3</td>
<td>16.1</td>
</tr>
<tr>
<td>Other</td>
<td>40</td>
<td>25.8</td>
</tr>
<tr>
<td>Prior Hospital Admission (%)</td>
<td>60</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>Less than 12 hours</td>
<td>More than 12 hours</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Compliant</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>20</td>
<td>10</td>
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<tr>
<td>Total</td>
<td>37</td>
<td>39</td>
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</tbody>
</table>

Using a Chi-square p<0.05
### TABLE 4 - Descriptive Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>TrMean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARMACY</td>
<td>70</td>
<td>3.756</td>
<td>3.540</td>
<td>3.659</td>
<td>2.170</td>
<td>0.259</td>
</tr>
<tr>
<td>Q13 - An</td>
<td>70</td>
<td>6.314</td>
<td>4.444</td>
<td>5.943</td>
<td>4.743</td>
<td>0.567</td>
</tr>
<tr>
<td>Q14 - An</td>
<td>70</td>
<td>4.342</td>
<td>3.950</td>
<td>4.251</td>
<td>1.892</td>
<td>0.226</td>
</tr>
<tr>
<td>Q5</td>
<td>70</td>
<td>0.328</td>
<td>0.000</td>
<td>0.3065</td>
<td>0.4731</td>
<td>0.0565</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Q1</th>
<th>Q3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARMACY</td>
<td>0.412</td>
<td>9.524</td>
<td>1.867</td>
<td>5.258</td>
</tr>
<tr>
<td>Q13 - An</td>
<td>0.556</td>
<td>26.667</td>
<td>3.333</td>
<td>8.000</td>
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<tr>
<td>Q14 - An</td>
<td>0.556</td>
<td>13.333</td>
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<tr>
<td>Q. 26</td>
<td>2.000</td>
<td>12.000</td>
<td>4.000</td>
<td>6.000</td>
</tr>
<tr>
<td>Q19-Ad</td>
<td>1.240</td>
<td>9.840</td>
<td>3.430</td>
<td>5.760</td>
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<tr>
<td>Q5</td>
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<td>1.0000</td>
<td>0.0000</td>
<td>1.0000</td>
</tr>
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</table>

### TABLE 5 - Correlations (Pearson)

<table>
<thead>
<tr>
<th></th>
<th>PHARMACY</th>
<th>Q13 - An</th>
<th>Q14 - An</th>
<th>Q. 26</th>
<th>Q19-Ad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q13 - An</td>
<td>0.216</td>
<td>0.461</td>
<td>0.366</td>
<td>0.366</td>
<td>0.980</td>
</tr>
<tr>
<td></td>
<td>0.072</td>
<td>0.004</td>
<td>0.002</td>
<td>0.002</td>
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<tr>
<td>Q14 - An</td>
<td>0.338</td>
<td>0.401</td>
<td>0.349</td>
<td>0.349</td>
<td>0.980</td>
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<td>0.004</td>
<td>0.001</td>
<td>0.003</td>
<td>0.003</td>
<td>0.000</td>
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<tr>
<td>Q. 26</td>
<td>0.360</td>
<td>0.334</td>
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<td>0.980</td>
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<td>0.002</td>
<td>0.005</td>
<td>0.003</td>
<td>0.003</td>
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<tr>
<td>Q19-Ad</td>
<td>-0.236</td>
<td>-0.073</td>
<td>-0.025</td>
<td>-0.208</td>
<td>-0.178</td>
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<tr>
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<td>-0.050</td>
<td>0.547</td>
<td>0.838</td>
<td>0.084</td>
<td>0.141</td>
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</table>

Cell Contents: Correlation
P-Value
The regression equation is
\[ \text{PHARMACY} = 2.04 + 0.169 \text{Q14 - An} + 0.275 \text{Q19-Ad} - 0.857 \text{Q5} \]

### Predictor Coef StDev T P
- **Constant** 2.0437 0.6682 3.06 0.003
- **Q14 - An** 0.16879 0.07891 2.14 0.036
- **Q19-Ad** 0.2751 0.1358 2.03 0.047
- **Q5** -0.8571 0.5090 -1.68 0.097

\[ S = 1.967 \quad \text{R-Sq = 21.5\%} \quad \text{R-Sq(adj) = 17.9\%} \]

### Analysis of Variance

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<tr>
<th>Source</th>
<th>DF</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>P</th>
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<tbody>
<tr>
<td>Regression</td>
<td>3</td>
<td>69.738</td>
<td>23.246</td>
<td>6.01</td>
<td>0.001</td>
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<tr>
<td>Residual Error</td>
<td>66</td>
<td>255.321</td>
<td>3.868</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>325.059</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>Seq SS</th>
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</thead>
<tbody>
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<td>Q14 - An</td>
<td>1</td>
<td>37.054</td>
</tr>
<tr>
<td>Q19-Ad</td>
<td>1</td>
<td>21.716</td>
</tr>
<tr>
<td>Q5</td>
<td>1</td>
<td>10.968</td>
</tr>
</tbody>
</table>

### Unusual Observations

<table>
<thead>
<tr>
<th>Obs</th>
<th>Q14 - An</th>
<th>PHARMACY</th>
<th>Fit</th>
<th>StDev</th>
<th>Fit</th>
<th>Residual</th>
<th>St Resid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.3</td>
<td>1.843</td>
<td>4.690</td>
<td>0.959</td>
<td>-2.847</td>
<td>-1.66 X</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>3.3</td>
<td>8.163</td>
<td>3.707</td>
<td>0.309</td>
<td>4.457</td>
<td>2.29R</td>
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</tr>
<tr>
<td>45</td>
<td>6.7</td>
<td>9.524</td>
<td>5.370</td>
<td>0.522</td>
<td>4.154</td>
<td>2.19R</td>
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<tr>
<td>58</td>
<td>1.1</td>
<td>6.316</td>
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<td>3.841</td>
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<tr>
<td>60</td>
<td>13.3</td>
<td>7.143</td>
<td>7.001</td>
<td>0.843</td>
<td>0.142</td>
<td>0.08 X</td>
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</tr>
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<td>66</td>
<td>13.3</td>
<td>7.143</td>
<td>5.638</td>
<td>0.828</td>
<td>1.505</td>
<td>0.84 X</td>
<td></td>
</tr>
</tbody>
</table>

R denotes an observation with a large standardized residual
X denotes an observation whose X value gives it large influence.
TABLE 7 - SENSITIVITY AND SPECIFICITY OF ACAS

COMPLIANCE ASSESSED BY PHARMACY

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>35</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>41</td>
<td>70</td>
</tr>
</tbody>
</table>

**SENSITIVITY** = \(\frac{12}{17+12} = 41\%\)

**SPECIFICITY** = \(\frac{35}{35+6} = 85\%\)

* N = non-compliant (positive result)
* C = compliant (negative result)
Asthmatic Compliance Assessment Survey (ACAS)

1. How long does a canister of your anti-inflammatory inhaler last?
   Number of doses in canister: _________
   Number of days canister lasts: _________
   Puffs/day: _________
   >70% Rx ➔ Compliant
   <70% Rx ➔ Non-compliant

2. When was the last time you took your short-acting bronchodilator?
   More than 12 hours ago ➔ Compliant
   Less than 12 hours ago ➔ Non-compliant

3. Everyone forgets to take their medication sometimes. What percent of doses do you estimate you have forgotten?
   Prescribed puffs/day: _________
   % forgotten: _________
   # doses forgotten: _________
   subtract
   Prescribed puffs/day: _________
   >70% Rx ➔ Compliant
   <70% Rx ➔ Non-compliant
   Adjusted puffs/day: _________
TTH Proposal #98-E164

Ms. Katherine Walewski
c- 4-011
Department of Respirology / Asthma Centre
The Toronto Hospital

Dear Ms. Walewski:

The protocol entitled "IMPROVING THE ASSESSMENT OF COMPLIANCE: Validating a Practical Instrument for Identifying Non-Compliance" and the consent forms have been reviewed by The Toronto Hospital Committee for Research on Human Subjects. The proposal is approved from an ethical standpoint.

If, during the course of the research, there are any serious adverse events, substantial changes in the approved protocol or any new information or developments which must be considered with respect to the study, these should be brought to the attention of the Committee.

Yours sincerely,

Gordon Hardacre, MD,CCFP,FCFP
Chair, The Toronto Hospital Committee for Research on Human Subjects

GH/bh

04/12/98

Date of Approval